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CONFORMATIONAL PROPERTIES OF GLYCOSIDIC LINKAGES

BY

Ⓒ DONALD B. COMPTON

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
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UNIVERSITY OF ALBERTA
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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

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To my wife Jan, for her patience and understanding during the preparation of this manuscript.

ABSTRACT

The effect of equatorial substituents, vicinal to the aglyconic carbon atom, on the preferred orientations for a 6-membered aglycon about the glycosidic bond system in solution is systematically investigated.

Data based on optical rotation and carbon-13 natural abundance studies of cyclohexyl D-glucopyranosides, substituted (1'R)- and (1'S)-*trans*-2'-cyclohexyl D-glucopyranosides and (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl D-glucopyranosides is presented and discussed in terms of the rotameric preferences for the orientation of the aglycon about the glucosidic linkage. It is found that these data can best be treated from a consideration of the three staggered conformers for the aglycon about the C-1' to O-1' bond, with the aglyconic carbon atom in all compounds assumed, by reason of the *exo* anomeric effect, to be *gauche* to the pyranoid ring oxygen atom.

The nature of the equatorial substituent in the 2' position of the cyclohexyl aglycon was changed from methyl, to hydroxyl, to chloro, to examine both the effects of changes in space requirements on the possible steric interactions and changes in the polarity of the substituent on possible dipole interactions, in the three staggered rotamers.

The 6-deoxy derivatives of the above mentioned cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides were synthesized and their optical rotations measured to study the effects of substitution on the orientation of the *exo*-cyclic C-5 hydroxymethyl function in solution.

ACKNOWLEDGEMENTS

The author expresses his appreciation to Professor R. U. Lemieux for his guidance, invaluable advice and understanding during the course of this work. He is grateful for the excellent research facilities provided by the University of Alberta.

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I. INTRODUCTION

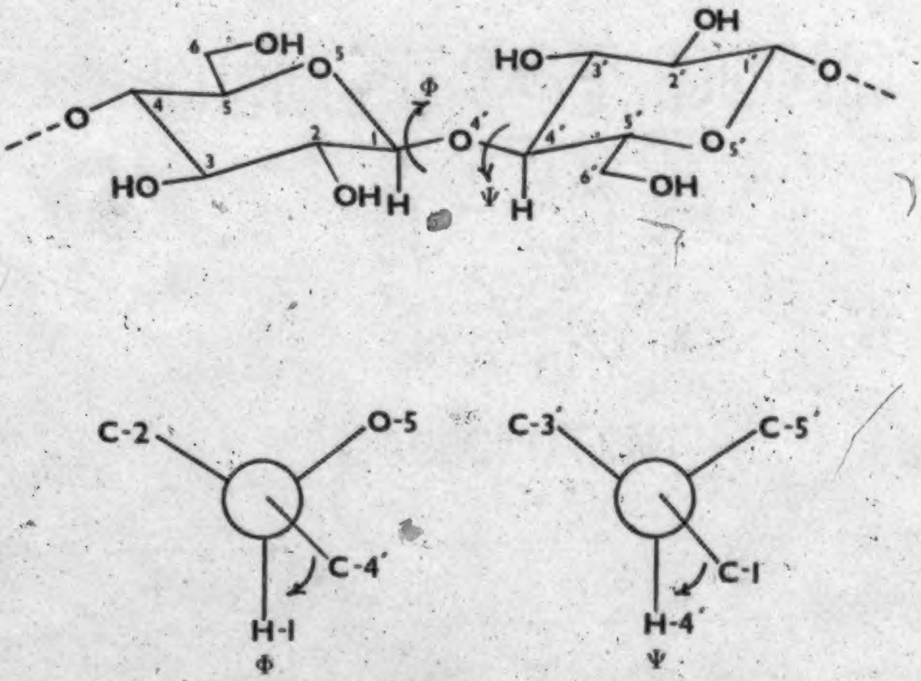
A. Conformational analysis of di- and polysaccharides

One of the most important functions of polysaccharides in Nature is their ability to form gels in a wide variety of situations within the bacterial, plant and animal kingdoms. Their important biological functions can be seen in the formation of the cell plate during division of plant cells (hence they contribute to wall texture and regulation of cell growth), in animal fluids and connective tissues, and in the bacterial capsule. They also have widespread commercial uses; particularly in foodstuffs, cosmetics, paper and textiles (1).

Gel formation can be explained simply as involving the association of chain segments of polymer molecules into a three dimensional framework that contains solvent in the interstices. These associated regions are known as junction zones and may be formed from two or more polymeric chains. The mechanism of gel formation, hence the physical and biological properties associated with them, can only be understood if the precise molecular arrangements and forces in the junction zones are known (1). The problem can further be reduced to a better understanding of polysaccharide conformations which would then lead to a better understanding of the nature of molecular interactions between polymers, including oligosaccharide antigenic determinants with antibodies (proteins).

Of crucial importance to the understanding of polysaccharide conformations is a knowledge of all the possible conformations about the inter-glycosidic linkages which are formed between two sugar residues (2). Recently, homopolymers of glucopyranose, galactopyranose, mannopyranose and arabinopyranose with various positions and configurations of linkage have been compared by model-building with the aid of a computer in an attempt to facilitate the prediction of simple rules for polysaccharide conformational analysis and possible correlation with biological activity (3).

Basically, the method of computer model-building assumes that the conformational properties of polysaccharides can be determined from two factors: the conformations of the individual monosaccharide residues and the relative conformations of respective pairs of monosaccharide residues linked glycosidically to each other. For each monosaccharide unit a set of atomic co-ordinates is derived from standard values of bond lengths and angles from X-ray crystallographic data and the premise that common sugar residues in polysaccharides will favour the $^4C_1$ conformation (4,5,6). The overall conformation of the polysaccharide chain would then depend only on the angles of rotation about the two bonds to each glycosidic oxygen atom. These rotational angles, termed ϕ and ψ, are illustrated for the β-D-cellobiose residue shown in Fig. 1 and are represented by the torsion angles C-4'/H-1 and C-1/H-4', respectively.


OH
6
O
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O
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3'
2'
1'
O
4'
5'
O
5'
6'
OH
C-2
O-5
C-4'
H-1
Φ
C-3'
C-5'
C-1
H-4'
Ψ

C

Fig. 1: The positive torsion angles, ϕ and ψ, for the β-D-cellobiose residue. The angles are positive since in each case the reference atoms describe a right-handed screw pattern (7).

The numbering scheme employed in Fig. 1 for the β-D-cellobiose residue is used throughout the remainder of this thesis. The atoms of the non-reducing sugar (glycosidic portion) are assigned unprimed numbers; those of the reducing portion (or the aglycon when referring to, for example, methyl or cyclohexyl D-glycopyranosides) are given primed numbers. In *O*-glycosides, the oxygen atom of the glycosidic bond is considered to be derived from the aglycon (or the reducing sugar where applicable) and, consequently, is numbered O'. The rotation used to denote torsion angles, for example A/B, defines the angle between two vicinal atoms, A and B, about a directed bond. The signs (positive or negative) of the torsion angles (see Fig. 1) are defined in the manner proposed by Brewster (7) and accepted by Klyne and Prelog (8).

Co-ordinates which refer to any conformation (ϕ, ψ) of the cellobiose residue are explored systematically by the computer by rotation about the O-4' to C-4' bond (changes in ψ) and about the O-4' to C-1 bond (changes in ϕ) in intervals of 10° throughout a 360° arc. In this way, $36^2 = 1296$ possible conformations are sampled. New co-ordinates are then calculated and used to characterize each of these conformations in terms of infringement of van der Waals radii and deviation of van der Waals energy minimum. The results are expressed in the form of a "conformational map" which shows the combinations of ϕ and ψ

giving no infringement of van der Waals radii. Thus an approximate area for the most favourable polymer conformation is estimated. The allowed values of ϕ and ψ are then further restricted by calculation of energy minima within the "conformational map" (9-15).

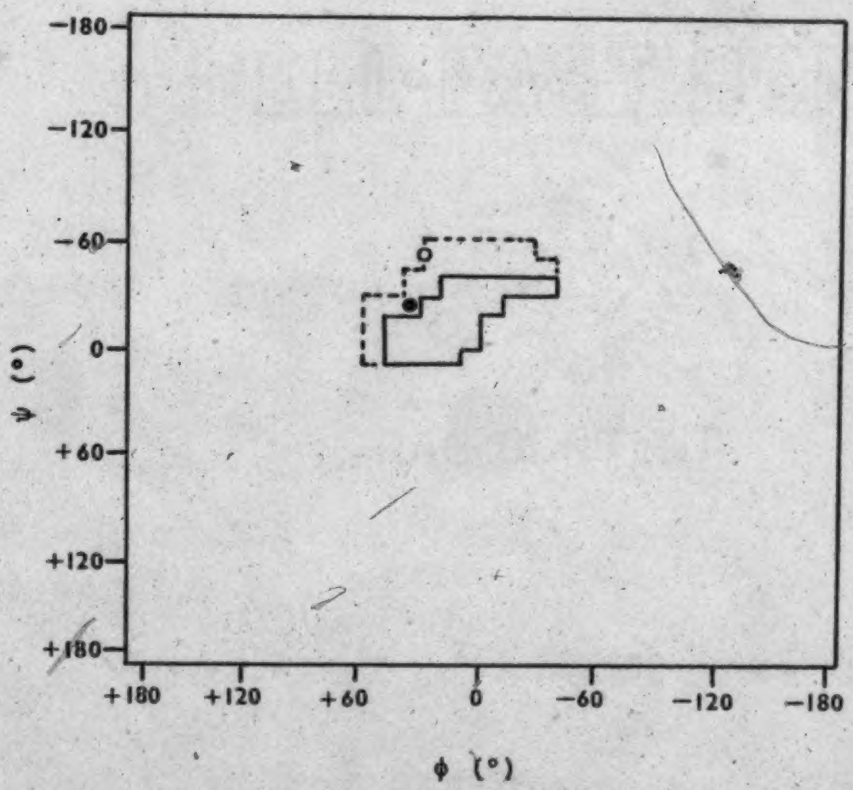


Fig. 2: The allowed (enclosed by solid lines) and marginally allowed (broken lines) conformations of the β-D-cellobiose residue. The point, ●, corresponds to the crystal structure of β-D-cellobiose and that, O, to the Hermans conformation of cellulose. Fully allowed conformations imply no non-bonded interactions between two atoms over distances less than the sum of their van der Waals radii. Marginally allowed conformations imply no non-bonded interactions over distances less than 0.9 times the sum of the van der Waals radii between two atoms.

An example of this computer model-building technique as an aid to understanding polysaccharide conformation is presented in Fig. 2 for cellulose (1,9). Of the 1296 possible conformations for the β-D-cellobiose residue of cellulose, 96% of these were rejected on the basis of steric compression of van der Waals radii. The remaining 4% lie in a well defined region illustrated by means of the "conformational map" shown. It is thus not surprising that the cellulose chain is somewhat stiff (16,17). On the basis of these computations, the conformation of β-D-cellobiose in the crystalline state corresponding to (+42°, -18°) for (ϕ, ψ) (18,19) was found to be near the energy minimum for non-bonded interactions, with the slight displacement toward higher potential energy favouring the formation of a hydrogen bond between O-5 and O-3'. Similar systematic exploration of all the possible conformations of cellulose was considered to indicate (1,9) that the "Hermans" or "bent-chain" conformation (20), corresponding to (+25°, -34°) for each (ϕ, ψ), is the only one which is relatively free from non-bonded interactions and also permits hydrogen bonding between O-5 and O-3' of contiguous residues. The total van der Waals energy is raised a little above the disaccharide values to allow for the twofold screw axis and thus to permit efficient packing of the polymer chains.

In a survey of general polysaccharide types (β- and α-D-glucans, -D-galactans, -D-mannans and -D-arabinans) differing in linkage positions, Rees (3) proposed several generalizations pertaining to polysaccharide conformational analysis with the aid of computer model-building previously discussed. Since this thesis is concerned primarily with an examination of the conformations of anomeric D-glucopyranosides, Rees' (3) observations will be restricted to those involving β- and α-D-glucans and -D-galactans. The observations will be further restricted by discussing only the conformations of the repeating disaccharide residues appearing in these polysaccharides. For example, observations pertaining to β-D-glucans with $1\rightarrow4'$ glucosidic linkages will refer to the 4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose residue.

To qualitatively assess the effect that substituent groups on the vicinal carbon atoms of the glycosidic linkage have on the allowed conformations about the glycosidic bond in these D-glucans and D-galactans, the torsion angles (ϕ, ψ), denoting one particular conformation, were averaged numerically for each polysaccharide over all allowed conformations. These average torsion angles are denoted as $\bar{\phi}$ and $\bar{\psi}$ and are defined in a like manner to that in Fig. 1.

These calculations showed that the torsion angle $\bar{\phi}$ was reasonably constant for most of the β-and α-linked disaccharide residues studied and was seen to be little affected by substituent groups on the carbons bonded to the carbon of the aglycon which forms the glycosidic linkage. Throughout this thesis, this carbon will be termed the aglyconic carbon, in contrast to the other carbon involved in a glycosidic linkage which is termed the anomeric carbon. This is shown pictorially in Fig. 3. Relatively large changes, however, were found to occur in the average values for $\bar{\psi}$ as the result of changes in the nature of the equatorial substituents vicinal to the aglyconic carbon. The changes occurring in $\bar{\psi}$ were rationalized in terms of rotation of the aglycon (reducing sugar portion) away from a larger substituent interaction or towards a smaller interaction.

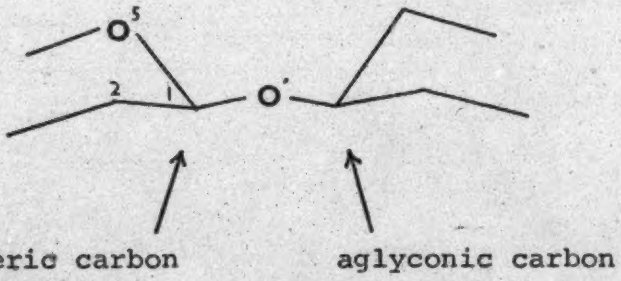
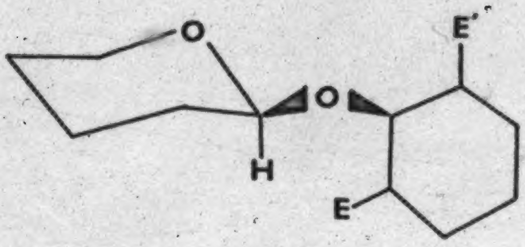


Fig. 3: Partial glycosidic structure showing the anomeric and aglyconic carbon atoms.

These conclusions regarding the effect of substitutions on the carbons adjacent to the aglyconic carbon are well demonstrated by a consideration of the three staggered orientations for the aglycon (ψ = +60°, -60°, and 180°) in anomeric D-glycopyranosides where the value for ϕ is kept at 60°. In this regard, it is well to keep in mind that the value of ϕ = 60° is favoured not only for steric reasons (minimum van der Waal conflict) but is also stabilized by the *exo* anomeric effect (21). Thus, it is reasonable to assume that, in general, congestion arising in a given conformation will likely be relieved mainly by a change in ψ rather than in ϕ and that ϕ will remain near 60°.

Figure 4 provides conformational formulas for the three staggered orientations of a six-membered aglycon in a β-D-glycopyranoside. These conformations here and throughout the thesis are referred to as the d, e and f conformations. It is difficult to present proper conformational formulas for these structures and it is best to use molecular models. Nevertheless, the formulas help to provide an appreciation of the important non-bonded interactions which occur as a result of the introduction of substituents on the carbons bonded to the aglyconic carbon. It is seen that in conformer d, an equatorial group at E



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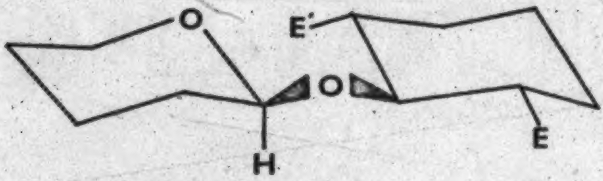

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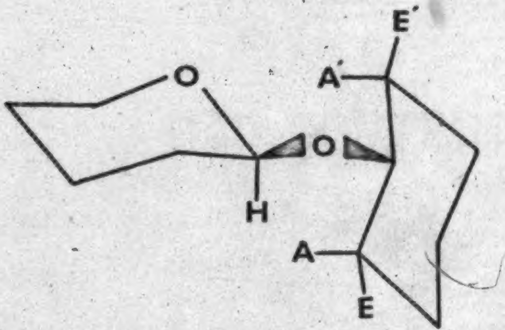

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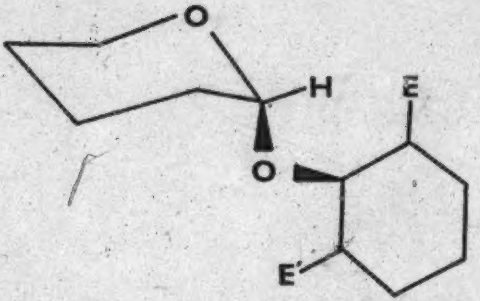
Fig. 4: Staggered conformations involving the changes in the torsion angle ψ for a β-D-glycopyranoside in the C1 conformation.

is directed toward the anomeric hydrogen. This group is well away from the pyranose ring in conformers e and f. An equatorial substituent, E', causes no non-bonded interactions in conformers d or f, but strong interactions in conformer e. Axial substituents do not interact with the pyranose ring except in conformer f, where the substituent A interacts strongly with the anomeric hydrogen and this conformation is likely not important in any glycosidic structure with ϕ maintained at 60°.

Figure 5 provides the conformational formulas for an α-D-glycopyranoside with staggered orientations for the six-membered aglycon ring. It is seen that an equatorial substituent, E, has a strong non-bonded interaction with the pyranose ring in conformers d and f but not in conformer e. On the other hand, an equatorial substituent, E', will destabilize none of these conformations. Axial substituents cause no interactions in conformer d, but a substituent at A' is unacceptable for conformer e. Substitution at both axial positions are forbidden for conformer f.

A more detailed conformational analysis of these conformations is presented in the Discussion with reference to an attempt to rationalize optical rotation and ^{13}C-n.m.r. data for the model compounds chosen for this study.



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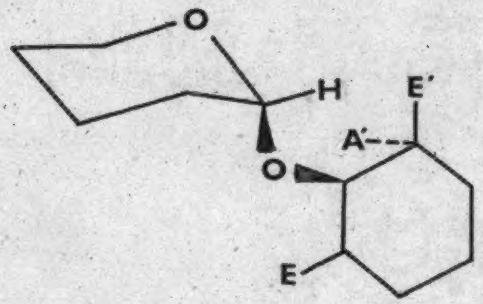

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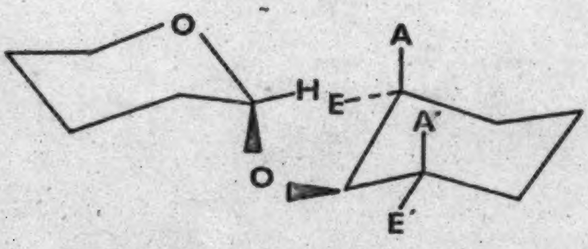

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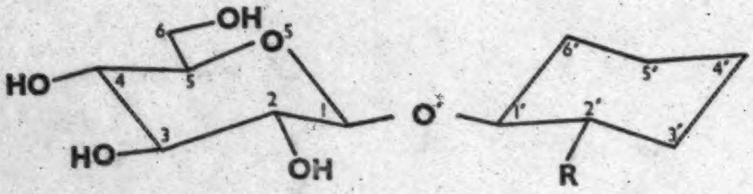
Fig. 5: Staggered conformations involving changes in the torsion angle ψ for an α-D-glycopyranoside in the Cl conformation.

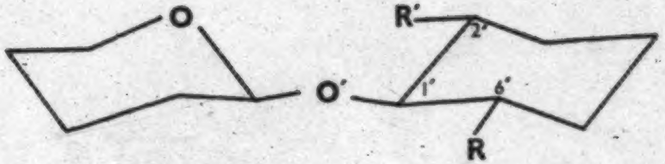
B. Objectives of this study

The preceding discussion has shown the importance of knowing the conformations about glycosidic linkages and the considerable interest shown in this basic problem of carbohydrate conformational analysis. Yet, to date, no systematic investigations of the structural features which can account for the preferred values for the torsion angles ϕ and ψ have been made. This study was therefore concerned with the synthesis of a number of model compounds expected to be useful in this regard.

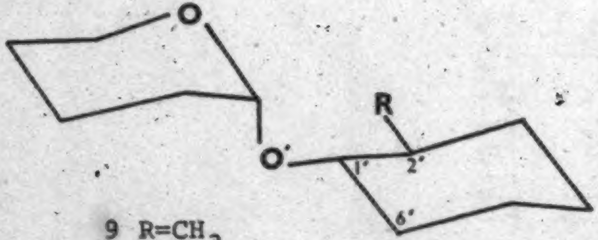
The research was restricted to cyclohexyl α- and β-D-glucopyranoside derivatives and a systematic study of the influences that equatorial substituents in the 2' and 6' positions of the aglycon have on the preferred conformations about the glucosidic bond. The model compounds, as illustrated in Figs. 6-7, were also chosen for this study due to their close structural similarity to α- and β-linked disaccharides , if it is assumed that cyclohexane and pyranose ring geometries are similar. X-ray crystal structure analyses of a number of sugar pyranoses indicate that the valence angle at the ring oxygen atom is mostly greater than that at the carbon atoms, which seems to counteract the effect of the two short carbon-oxygen bonds when compared with the carbon-carbon bonds of cyclohexane (2,5).


OH
O5
6
HO
4
5
2
1
O
HO
3
OH
1'
2'
6'
5'
4'
3'
R

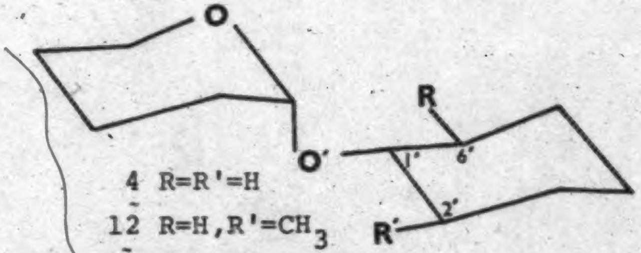
5 R=CH_3
13 R=OH
21 R=Cl



2 R=R'=H
6 R=H,R'=CH_3
14 R=H,R'=OH
22 R=H,R'=Cl
30 R=CH_3,R'=CH_3

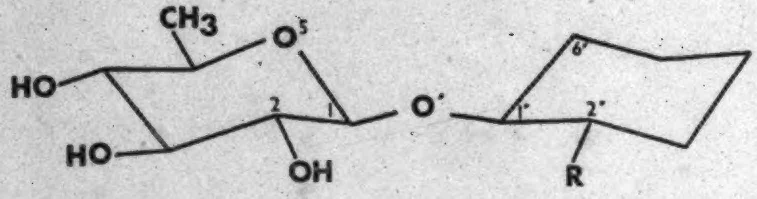


9 R=CH_3
17 R=OH
25 R=Cl

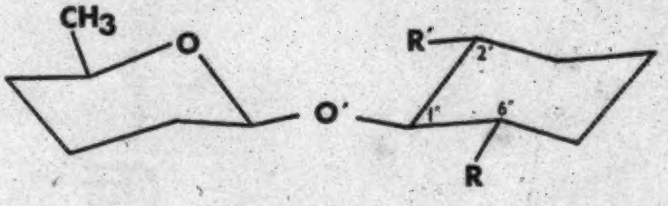


4 R=R'=H
12 R=H,R'=CH_3
20 R=H,R'=OH
28 R=H,R'=Cl
32 R=CH_3,R'=CH_3

Fig. 6: D-Glucopyranosides chosen for a study of the conformational properties about the glucosidic linkage in solution.

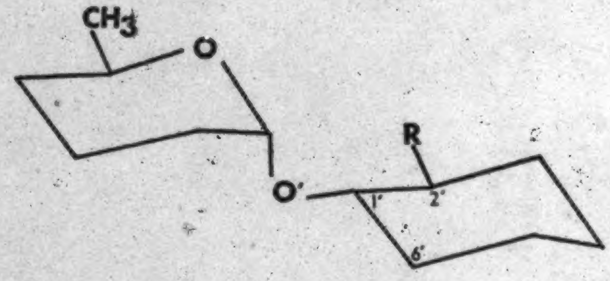

CH3
O5
HO
HO
2
1
OH
O'
1'
2'
6'
R

44 R=CH_3

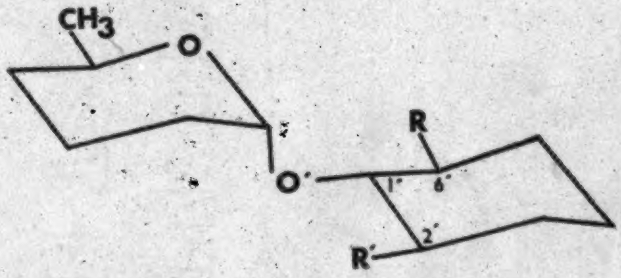

CH3
O
O'
R'
2'
1'
6'
R

37 R=R'=H

51 R=H,R'=CH_3



46 R=CH_3


CH3
O
O'
R
1'
6'
2'
R'

39 R=R'=H

53 R=H,R'=CH_3

Fig. 7: 6-Deoxy derivatives of anomeric cyclohexyl D-glucopyranosides.

From this, it may be inferred that distances between the ring carbon atoms of the pyranose ring are not very different from those in the regular cyclohexane ring. Furthermore, conformational free energy calculations (22) and X-ray and neutron diffraction studies (23) on hexopyranoid sugar derivatives with the *gluco* configuration indicate that the $^4C_1$ conformers are the more favoured form in solution. Thus, any changes occurring in the conformation about the glucosidic linkage from one model compound to another should be due solely to the nature of the equatorially disposed substituents (R and R') on the aglycon, as the conformation of the glucose ring is expected to be the same in all cases.

The principle measurement used is optical rotation since it can be expected (24) that changes in the torsion angles denoted by ϕ and ψ, as the result of changes in the nature of R and R', would strongly affect the sign and magnitude of this molecular property. However, the recent evidence for the profound chemical shifts for carbon-13 atoms which occur through steric compression (25-30) suggested that carbon-13 n.m.r. could also likely aid in assessing conformational changes.

In view of the non-polar character of the methylcyclohexyl aglycon it was hoped that the preferred conformations for compounds 5, 6, 9 and 12 would result mainly from steric interactions and that the conformations found in the crystalline state could reflect those in aqueous solution. Therefore, an effort was made (31) to achieve the X-ray crystallographic structures for these model compounds as a possible aid in determining the conformations about the glucosidic bond system in these molecules.

The nature of the equatorially oriented substituents (R and R') was changed from methyl, to hydroxyl, to chloro, in order to examine the effects of both changes in space requirements on the possible steric interactions and of changes in the polarity of the substituent on possible dipole interactions including intramolecular hydrogen bonding and hydrogen bonding with the solvent about the glucosidic linkage. The 6-deoxy derivatives of the above mentioned glucopyranosides **37**, **39**, **44**, **46**, **51** and **53** were synthesized and their optical rotations measured to determine whether or not the contribution by the *exo*-cyclic C-5 hydroxymethyl group to molecular rotation remained constant with changes in the structure of the aglycon and changes in configuration at the anomeric center.

It is necessary that the range of allowed values for the torsion angles ϕ and ψ be restricted in order to facilitate the consideration of rotameric preferences about the glucosidic bond system. Therefore, the remaining portion of this introduction will center mainly on observations and physical evidence that restrict the number of possible conformations about the glycosidic linkage to be considered.

C. The prefered rotamers for the aglycon about the anomeric bond in α- and β-D-glycopyranosides

1. The *exo* anomeric effect.

The enhanced stability of electronegative (acetoxy, halogeno, and methoxy) substituents associated with the preference for axial over equatorial substitution on C-1 of a pyranoid ring was first discussed by Edward (32) on the basis of assumed conformations. The preference for polar aglycon groups to assume an axial disposition was firmly established through n.m.r. studies (33), and the phenomenon termed the "anomeric effect" by Lemieux and Chü (34,35). The term "generalized anomeric effect" was introduced (36) to explain similar observations in substituted tetrahydropyrans (37-43), steroids (44) and heterocyclic ring systems including 1,3- and 1,4-dioxanes (45-48), 1,4-dithianes (49) and 1,4-thioxanes (50). The many differing views (32,34-35, 40,51-54) on the nature and origins of the anomeric effect have been the subject of a recent review by Martin (55) and are similarly discussed in a recent book by Stoddart (56) on carbohydrate conformational analysis. The anomeric effect has also been the subject of several recent theoretical investigations involving *ab initio* quantum mechanical calculations for fluoromethanol (57) and methanediol (58-59), the simplest model compounds expected to show such an effect.

When considering the preferred orientations of the aglycon in α- and β-D-glycopyranosides, the aglycon should tend to adopt the α-a and β-a conformations shown in Fig. 8, respectively, both for reasons of the anomeric effect and steric considerations (60-61). This apparent preference for the R group to adopt a *syn-clinal* orientation with respect to O-5 and *anti*-parallel to C-2 in anomeric D-glycopyranosides has been termed the *exo* anomeric effect by Lemieux, Pavia et al. (21). Indeed, X-ray crystallographic studies (62-64) on a number of glycosidic structures have found the aglycons to be in these orientations. However, in solution, the possibility exists that other conformations with staggered orientations for the aglycon about the anomeric center might be important and these also are shown in Fig. 8. The relative importance of the three staggered orientations for the aglycon in D-glycopyranosides is discussed below with reference to the conformers for methyl α- and β-D-glucopyranoside.

Consider, first of all, the staggered conformers for methyl α-D-glucopyranoside shown in Fig. 9. It is seen

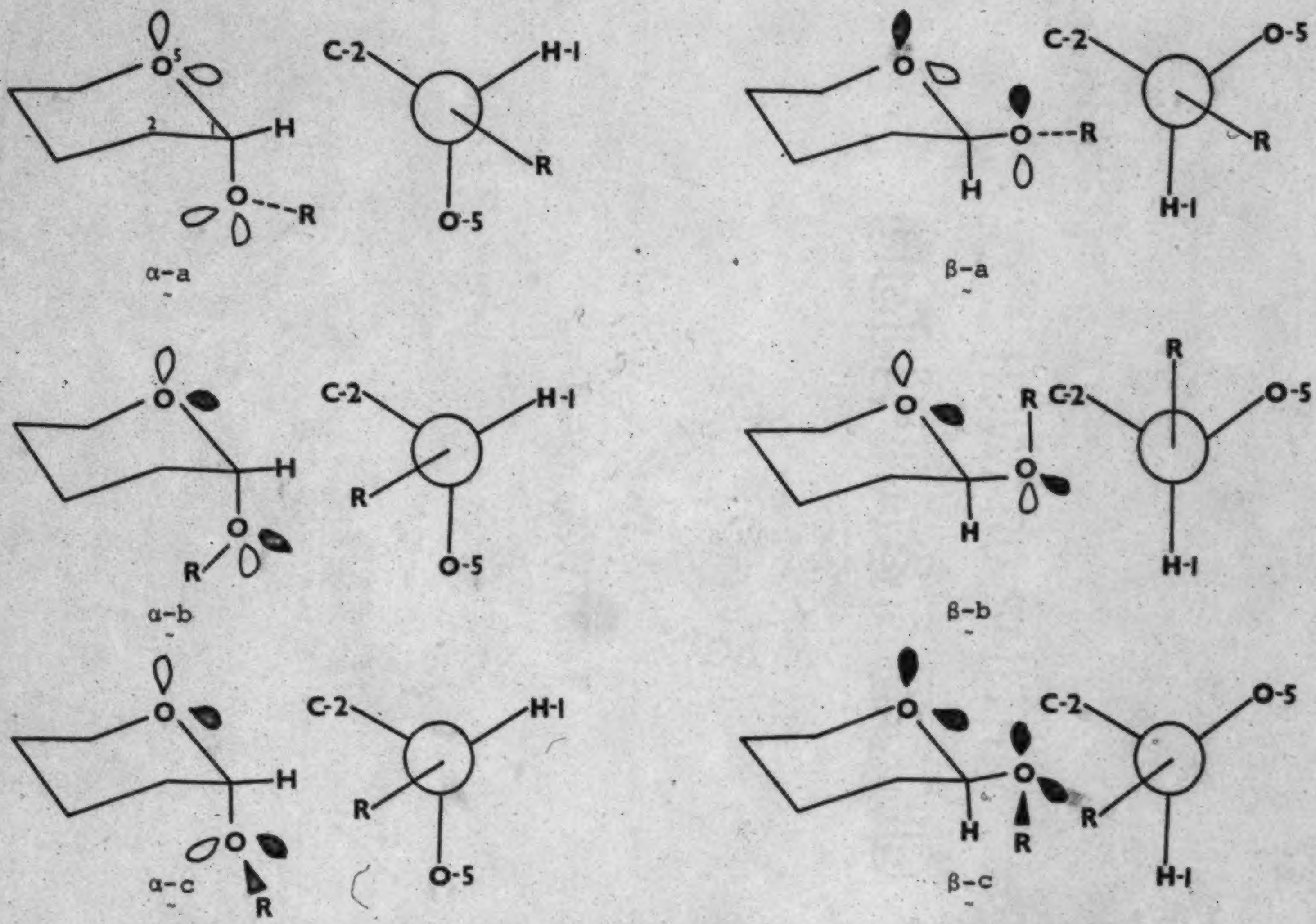

O
5
2
1
H
O
R
C-2
H-1
R
O-5
α-a
C-2
O-5
O
O
R
H
R
H-1
β-a
O
H
O
R
C-2
H-1
R
O-5
α-b
R
O
R
C-2
O-5
O
H
H-1
β-b
O
H
O
R
C-2
H-1
R
O-5
α-c
O
C-2
O-5
O
H
R
R
H-1
β-c

Fig. 8: The six possible staggered conformers for D-glycopyranosides.

at once that steric and non-bonded interactions strongly favour the α-a conformer. This follows since the α-c conformer not only does not conform to the stabilizing influence of the *exo* anomeric effect but has the methyl group in *syn*-diaxial-like relationship with the 2-hydroxyl group. Thus, it must be expected that the α-c conformer is over 4 Kcal/mole less stable than the α-a conformer. In the case of the α-b conformer, the methyl group is in *syn*-diaxial-like relationship both with H-3 and H-5. Thus, although this conformation has the benefit of the anomeric effect, it must also be several Kcal/mole less stable than the α-a conformer. Evidence based on optical rotation data will be presented later on which confirms these conclusions.

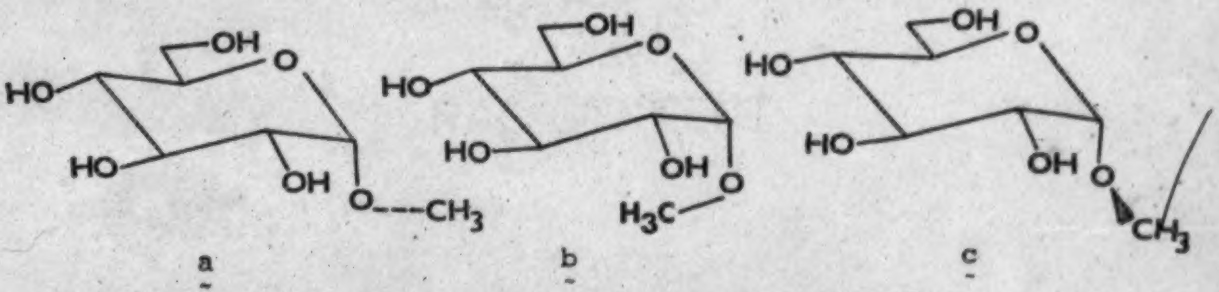


Fig. 9: The three staggered conformers for the aglycon in methyl α-D-glucopyranoside.

The situation with regard to the staggered conformers for methyl β-D-glucopyranoside shown in Fig. 10 is not as straightforward. In this case, the β-c conformer does not have the benefit of the *exo* anomeric effect and has the methyl group in *syn*-diaxial-like relationship with the 2-hydroxy group. Clearly, this conformer is several Kcal/mole less stable than β-a. Although the β-a and β-b conformers must at this time be considered as equivalent with regard to the *exo* anomeric effect, steric considerations favour the β-a conformer over the β-c conformer. However, the driving force for the conversion of β-b to β-a cannot be expected to be more than about 2 Kcal/mole (that is, about the A value for a methyl group on a cyclohexane ring (56). Therefore, to assume that the β-b conformer has a negligible contribution requires experimental evidence. Evidence in support of this contention is provided by a consideration of the rotations for the methyl glycopyranosides shown in Table 1.

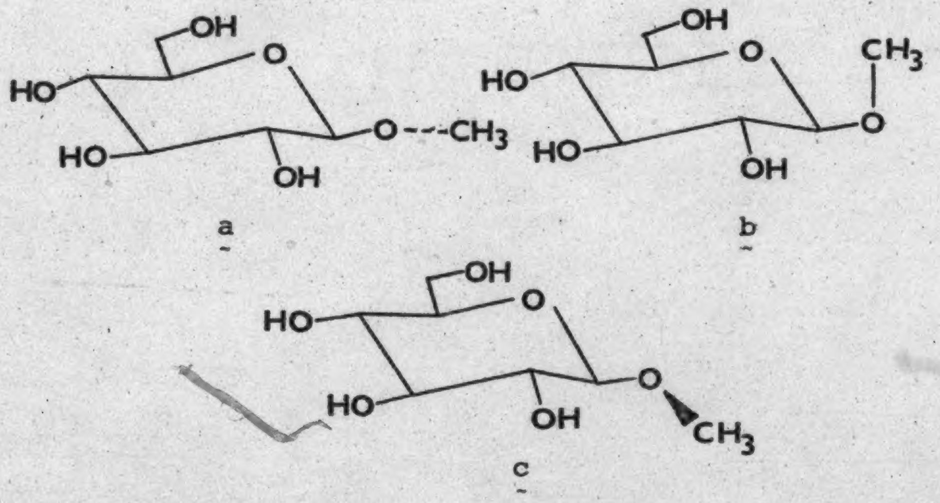


Fig. 10: The three staggered conformers for the aglycon in methyl β-D-glucopyranoside.

TABLE 1

A comparison of the molecular rotations for some methyl D-glycopyranosides and their corresponding D-glycopyranoses

		Molecular Rotations (°)*	
D-Glucopyranose		Methyl D-glycopyranoside	Diff.
α-D-*gluco*	+202	+309	+107
α-D-*manno*	+ 53	+154	+101
β-D-*gluco*	+ 34	- 66	-100
β-D-*manno*	- 31	-135	-104

---

* Values for the molecular rotations were reported in a paper by Lemieux and Martin (65) and references quoted therein.

As shown in this table, the differences in molecular rotation between the methyl β-D-glycopyranosides and their corresponding β-D-glycopyranoses is constant at -102 ± 2°. If the β-b conformer existed to any appreciable extent in solution, it might be expected that this conformer would be more favourable in the glycopyranoside with the *gluco* configuration as the β-b conformer in methyl β-D-mannopyranoside has the methoxy group *syn*-diaxial to the C-2 hydroxy group and would be less stable due to steric considerations. However, due to the constant difference in molecular rotation observed, it must be argued that the β-b conformer is negligible in methyl β-D-glucopyranoside as well and that the aglycon prefers the orientation in the a conformer for both β-D-glycopyranosides. Moreover, since the magnitude of this difference in molecular rotation is the same, and constant, for the α-linked derivatives, the α-a conformer must also exist almost exclusively in solution.

Similar conclusions as to the rotameric preferences for the aglycon were drawn by de Hoog and co-workers (66) by dipole moment measurements and ^{1}H coupling constant data for the equilibrium of axially and equatorially substituted 2-alkoxy-tetrahydropyrans. The authors found that out of the six possible staggered conformers for the alkoxy substituent (cf. Fig. 8), only two predominated, these being α-a for axial anomers and β-a for equatorial anomers.

2. X-ray crystallographic and vicinal carbon-13 proton coupling studies.

From an analysis of the torsion angles about the glycosidic linkages in mono- and disaccharides in the crystalline state it is possible, if these angles persist in solution, to predict the favoured orientation for the aglycon about the anomeric bond in solution. The appropriate torsion angle ϕ observed in the known crystal structures of anomeric methyl glycopyranosides is presented in Table 2. As is seen, the range of values for the torsion angle ϕ, which constitutes an expression of the *exo* anomeric effect, are constant for the anomeric D-glycopyranosides shown. Specifically, ϕ has values close to -60° for the α-anomers and values close to +50° for the β-anomers. These values for the torsion angle define the orientation of the methyl aglycon in the $\underset{\sim}{\alpha\text{-a}}$ and $\underset{\sim}{\beta\text{-a}}$ conformers, respectively, predicted to exist most favourably in solution.

One might argue that this correspondence between the predicted conformation in solution and that observed in the solid state by X-Ray analysis is fortuitous due to the fact that directional intermolecular forces in the solid state play an important part in establishing the structure, and hence the conformation of the molecule. However, in the simple methyl glycosides, the orientation of the methyl

TABLE 2

Torsion angle ϕ in some D-glycopyranosides defining the orientation of the methyl aglycon

Compound	Ref.	ϕ (°)*
Me α-D-glucopyranoside	62	-57
Me 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside	67	-50.5
Me α-D-galactopyranoside	68a	-57
Me α-D-mannopyranoside	68b	-59
Me α-D-altropyranoside	68c	-56
Me β-xylopyranoside	69	+47.7
Me 1-thio-β-D-xylopyranoside	70	+55.2
Me β-maltopyranoside	63	+50.8
Me β-D-cellobioside	71	+43.8

* These values were calculated from the torsion angle defined by the aglyconic carbon and the ring oxygen atom by subtracting 120° and, therefore, are expected to approximate the value for ϕ.

TABLE 3

Torsion angle ϕ in some disaccharides defining the orientation of the aglycon

Compound	Ref.	ϕ (°)*
O-α-D-galactopyranosyl-(1→6) α-D-glucopyranosyl residue of Raffinose Pentahydrate	72	-48.2
O-α-D-galactopyranosyl-(1→6)-β-D-fructofuranosyl residue of Planteose Dihydrate	73	-53.5
Methyl β-D-maltopyranoside	63	- 9.2
O-α-D-glucopyranosyl-(1→1)-α-D-glucopyranoside	74	+58.3 +45.3
β-D-cellobiose	19	+43.8
Methyl β-D-cellobioside	71	+31.1

---

* These values were calculated from the torsion angle defined by the aglyconic carbon and the ring oxygen atom by subtracting 120° and, therefore, are expected to approximate the value for ϕ.

group is not subject to directional intermolecular hydrogen bonding and the conformation of the molecule in the solid state may well approximate that predicted to exist most favourably in solution.

The values for the torsion angle ϕ observed in the known crystal structures of several di- and trisaccharides are presented separately in Table 3, for unlike simple methyl glycopyranosides, the conformations of these more complex sugars in the solid state are subject to directional intermolecular hydrogen bonding and crystal packing forces. As expected, the values for the torsion angle ϕ are more varied than those observed for simple methyl glycopyranosides. In the case of the α-(1→6)- and -(1→1)-linked disaccharides, the values of ϕ show relatively little deviation from the value of -60° as predicted by the *exo* anomeric effect. For the β- and α-(1→4)-linked disaccharides, considerable deviation from ϕ=60° is noted and is attributed to the intermolecular and intramolecular hydrogen bonding found in the solid state for these molecules. The torsion angle between the aglyconic carbon and H-1 (ϕ) is much smaller to allow for the formation of an intramolecular hydrogen bond between O-3' and O-5 in both methyl β-D-cellobioside and β-D-cellobiose and between O-3' and O-2 in methyl β-D-maltopyranoside. Differences in crystal packing forces could also be reflected in these changes in ϕ values.

Further evidence for preferred rotameric conformations can be deduced from studies of vicinal ^{13}C to proton coupling over the anomeric bond. Presently under investigation (75) is a study of vicinal ^{13}C coupling constants for alkyl α- and β-D-glucopyranosides, their 2-deoxy derivatives and methyl α- and β-D-mannopyranosides. The most constant factor observed in the study was that the coupling constants of the β-glycosides were greater than those of the corresponding α-glycosides. The absence of a severe depression in the size of the vicinal coupling constant for methyl β-D-mannopyranoside ruled out the interpretation that the larger coupling constants observed in the β-linked glycosides was due to the presence of a substantial proportion of the β-b rotamer in solution. The presence of an axial hydroxyl group at C-2 in methyl β-D-mannopyranoside would be expected to reduce the population of the β-b rotamer to insignificant levels by reason of the 1,3-*syn*-diaxial interaction between the methyl and hydroxyl groups in the rotamer. A preliminary explanation offered was that the torsion angle ϕ was less than 60° and hence the vicinal coupling constant would be expected to be somewhat larger if the coupling constants did, indeed, depend on the torsion angle (76). Support for this explanation can be derived from X-ray crystallographic data and nuclear Overhauser experiments.

Nuclear Overhauser studies on methyl α- and β-D-glucopyranosides and their 6-deoxy derivatives (75) only showed an enhancement ratio for the β-anomers, thus indicating that the methyl protons in the β-glycoside were closer to H-1 and hence the explanation that ϕ was less than 60°

A possible explanation for the observation that the vicinal coupling constants for α-D-glycopyranosides was in all cases smaller than for the β-anomers was also derived from X-ray crystallographic data and the negative result observed in nuclear Overhauser experiments. X-ray data shows that in most cases the torsional angle ϕ has values close to 60°. If this angle persists in solution, then it is expected that the coupling constant for α-D-glycopyranosides should be smaller when compared to the torsion angle ϕ = 50° for β-glycopyranosides.

D. Empirical rules for the prediction of carbohydrate optical rotations

1. Conformational asymmetry.

In the theoretical investigation of optical rotation to follow, contributions to rotation from individual asymmetric carbon atoms are considered to be small or negligible.

These are independent of conformational geometry and hence independent of conformational distributions.

According to Whiffen (77) and Brewster (7), the large rotations of saturated cyclic compounds can be expected, for the most part, to arise from conformational, rather than atomic asymmetry. The simplest examples of asymmetric conformational units, the three-bond (4 atom) chains, are shown in Fig. 11. It was shown that such units can give rise to optical activity and it was proposed that the magnitude of the optical activity is a function of the sine of the torsion angle θ (24). The units that are considered in these empirical rules to be discussed originate in staggered conformations where θ is ideally 60°, -60°, or 180°.

2. The empirical rules of Lemieux and Martin.

Lemieux and Martin (65), following Whiffen's procedure (77), recently proposed what appeared to be a convenient set of simplified rules for the estimation of asymmetric three-bond conformational units formed by terminal carbon and oxygen atoms in a *gauche* relationship. Units that terminated in hydrogen or hydrogens were considered to make a negligible contribution to rotatory power. They required only three parameters to describe the three bond asymmetric unit defined as O/O, O/C and C_o/O. A

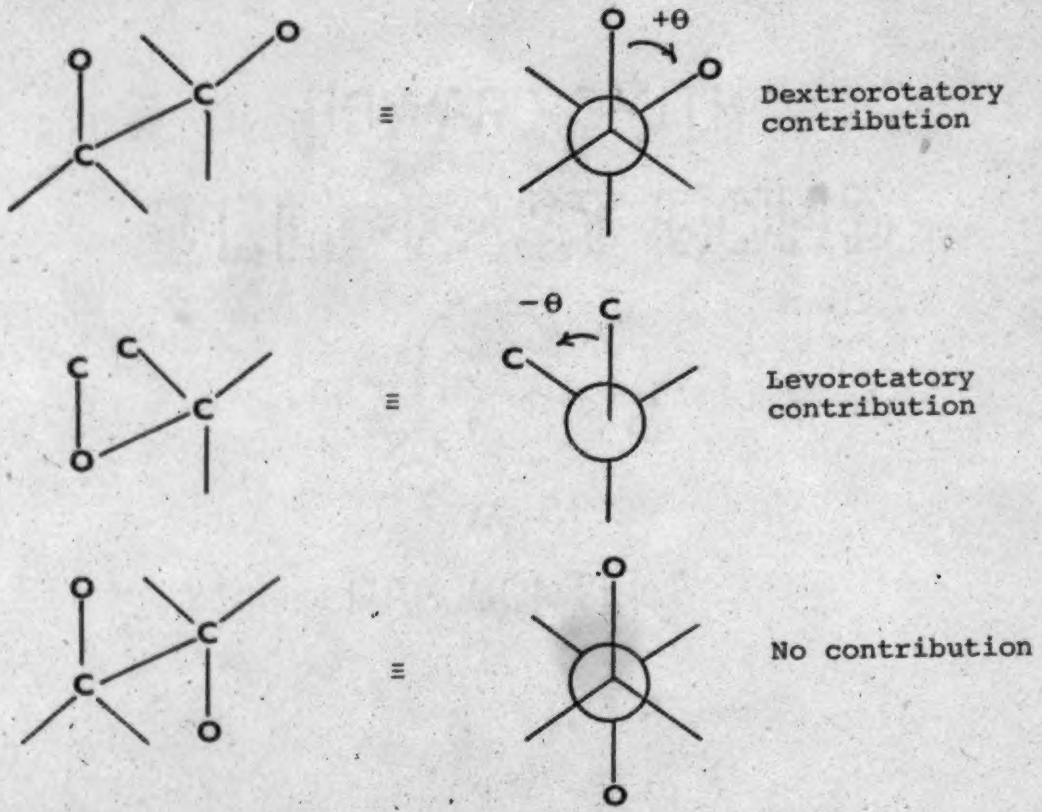

O
+θ
O
C
C
O
≡
Dextrorotatory
contribution
−θ
C
C
C
C
O
≡
Levorotatory
contribution
O
C
C
O
≡
No contribution

Fig. 11: Examples of three-bond units of conformational asymmetry.

fourth unit, C_O/C was needed to calculate the molecular rotations of *O*-methyl derivatives of pyranoid compounds.

This theoretical treatment is to be used in the Discussion in an attempt to calculate the rotamer populations for the orientation of the cyclohexyl ring about the glucopyranoside linkage (cf. conformers d, e and f shown in Figs. 4-5) for the model compounds chosen for this study. Only Lemieux and Martin's (65) original value of ±115° for the C_O/O rotatory contribution is maintained. The values for the O/O and C/O rotatory contributions as originally assigned are different. Contributions to molecular rotation from these parameters are assigned by a consideration of the molecular rotations observed for the enantiomeric substituted cyclohexanols shown in Table 4. In these molecules, the only expected contribution to rotation is the asymmetric conformational unit defined by the hydroxy group and the substituent at C-2 in *gauche* orientation. Therefore, the values assigned to the O/O and C/O parameters are ±55° and ±50°, respectively. In the empirical treatment of Lemieux and Martin (65), no mention was made of the possible rotatory contribution from a chlorine atom and an oxygen atom in a *gauche* relationship. From the molecular rotation observed for (-)-*trans*-2-chlorocyclohexanol, a new parameter, Cl/O, is defined and given the value of ±55°. The value given to the C_O/C asymmetric conformational unit

TABLE 4

Molecular rotations for a number of enantiomeric cyclohexanols

Alcohol	$[M]_D$ (°)	Ref.
(-)-*trans*-1,2-Cyclohexanediol	-54.0	78
(-)-*trans*-2-Methylcyclohexanol	-48.9	79
(-)-*trans*-2-Chlorocyclohexanol	-53.8	80

will be assigned in the Discussion from a consideration of the rotamer populations for (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (9). These parameters to be used in subsequent calculations are summarized in Table 5 along with their assigned contributory values to molecular rotation.

TABLE 5

Values for the 4 atom asymmetric conformational units to be used in the calculation of rotamer populations

Atoms in *gauche* relationship	Contribution to molecular rotation (°)
O/O	+ 55
C/O	+ 50
Cl/O	+ 55
C_o/O	+115

3. Calculation of a linkage rotation.

In an attempt to use optical rotation to estimate and relate to the torsion angles ϕ and ψ used in connection with computer model-building discussed in Section I-A, Rees (81) derived a parameter known as the "linkage rotation," $[\Lambda]_D$, within the context of Kauzmann's (82) principle of pair-wise interactions.

The value of $[\Lambda]$ at a given wavelength, which represents the optical rotation due to interactions across the glycosidic linkage minus any contributions from the individual monosaccharide units, is given by the following equation:

$$[\Lambda]_{obs} = [M_{NR}] - [M_{MeN}] + [M_R]$$

where

$[\Lambda]_{obs}$ ≡ observed linkage rotation

$[M_{NR}]$ ≡ molecular rotation for a given disaccharide which contains a non-reducing (N) and a reducing (R) residue

$[M_{MeN}]$ ≡ molecular rotation of the methyl glycoside of N having the same anomeric configuration as the disaccharide

$[M_R]$ ≡ rotation of the reducing sugar.

Rees also showed that the linkage rotation could be related to the linkage parameters (ϕ and ψ) by using the earlier observations of Whiffen (77) and Brewster (24) that each four atom chain, in this case about the glycosidic linkage, makes a contribution to rotation which depends on the sine of the torsion angle. The appropriate relationships for β- and α-linked disaccharides are, respectively:

$$[\Lambda]_D^\beta = 105-120 (\sin \phi + \psi)$$

$$[\Lambda]_D^\alpha = -105-120 (\sin \phi + \psi)$$

Using values of ϕ and ψ obtained from crystal structure data, Rees predicted to within a few degrees, the linkage rotations of several disaccharides. For example, the appropriate values from crystal structure data for β-D-cellobiose are $\phi = 42°$ and $\psi = -18°$, which leads to $[\Lambda calc]_D^\beta = +62°$ in remarkably good agreement with $[\Lambda obs]_D^\beta = +59°$. For β-D-lactose, $\phi = 31°$ and $\psi = -25°$, and thus $[\Lambda calc]_D^\beta = +94°$ as compared with $[\Lambda obs]_D^\beta = +95°$

This close agreement between $[\Lambda calc]_D$ and $[\Lambda obs]_D$ must, however, be questioned for a number of reasons. The values for the torsion angles ϕ and ψ are taken directly from X-ray crystal data and used to calculate rotation which is then compared with the observed linkage rotation of a disaccharide in solution. Any agreement must therefore, be fortuitous since it is expected that the torsion angles found in the solid state could well deviate from those found in solution. As mentioned earlier, directional intermolecular hydrogen bonding and crystal packing forces are expected to strongly influence the conformation of the molecule, hence ϕ and ψ, in the solid state. It was also discussed that in solution, the orientation of the aglycon about the anomeric bond would tend to approach values of $\phi = 60°$, both for reasons of the *exo* anomeric effect and steric considerations. Using this value of $\phi = 60°$ and the value of $[\Lambda obs]_D$ for β-D-cellobiose and β-D-lactose, new values of ψ for each disaccharide may be calculated. The appropriate calculated values for β-D-cellobiose and β-D-lactose are, respectively, $\psi = 30°$ and $\psi = 49°$. As noted, these values differ significantly from those observed from X-ray crystal data and could possibly be more favoured in solution due to the greater tendency toward a staggered orientation of the non-reducing sugar portion about the glycosidic linkage. For that matter, the nature of the equations for the calculations of a linkage rotation lead to a number of solutions depending on the values chosen for the torsion angles ϕ and ψ and give good agreement with $[\Lambda obs]_D$.

It is thus seen that the calculation of a linkage rotation depends on the values chosen for ϕ and ψ.

Therefore, the use of this parameter is predicting the orientational tendencies about the glycosidic bond system must remain, at best, only an approximation.

E. Carbon-13 chemical shifts

Before preceding to a review of carbon-13 n.m.r. studies of mono and disaccharides relevant to this study, it is essential to mention briefly the work done on substituted cyclohexanes and cyclohexanols. The material presented here is by no means complete, but is simply intended to mention the highlights of substitution and steric interactions on the nature of the ^{13}C chemical shift. More extensive treatment can be found in recent books by Levy and Nelson (83) and Strothers (84).

Carbon-13 chemical shifts in the cyclohexane series are influenced strongly by conformational and geometrical factors (25-27). The methylcyclohexanes, for which extensive data are available (27), provide a particularly clear illustration of the kind of effects that occur. In general, individual ^{13}C nuclei of a compound may experience either deshielding (shifts to lower field) or increased shielding (shifts to higher field), the direction and magnitude of which is determined by the position and orientation of the methyl substituents. Enhanced shielding is attributed mainly to steric hindrance associated with *gauche* interactions of the methyl groups, and deshielding to relief of these interactions (27-30). For example, several ^{13}C nuclei of an isomer containing an axial methyl group come into resonance at higher field than when the group is equatorial, similarly, vicinal methyl groups are associated with greater shielding than are 1,3- or 1,4-arrangements (27).

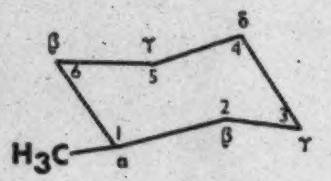
The effects of methyl substitution on the shifts of alicyclic carbon nuclei as observed by Dalling and Grant (27) in a series of methylated cyclohexanes are shown in Table 6. Substantial differences in substitutional effects of an axial or equatorial methyl group on the α, β and γ carbons are observed. The effect is especially pronounced at the α and γ carbons, the resonances of which are ~ 5 ppm to higher field over what might otherwise be expected when the methyl group is axial. With reference to Fig. 12, it is seen that the C-1 to CH_3 bond in the axial orientation is *gauche* with respect to both the C-2 to C-3 and C-5 to C-6 bonds, but *anti* to these bonds when the methyl group is equatorial. Presumably, non-bonded interactions between the axial methyl group and the axial hydrogens at C-3 and C-5 are sufficient to perturb the electron distribution about these nuclei such that their shielding is increased. Transmission of this effect along the CH_3 to C-1 bond may be suggested to account

TABLE 6

Methyl substituent parameters for substituted cyclohexanes

Substituent	Parameters (ppm)*			
	α	β	γ	δ
eq. CH_3	+5.6 ± 0.2	+8.9 ± 0.1	0.0 ± 0.6	-0.3 ± 0.2
ax. CH_3	+1.1 ± 0.4	+5.2 ± 0.3	-5.4 ± 0.2	-0.1 ± 0.3
Geminal $(CH_3)_2$	-3.4 ± 0.6	-1.2 ± 0.4		
Vicinal $(CH_3)_2$ dieq.	-2.3 ± 0.3			
ax., eq.	-3.1 ± 0.6			

* The parameters α, β, γ and δ refer to the substitution as given below.



for the observed shielding at the α-carbon. The difference of ~ 3 ppm between the effects for axial and equatorial substitution on the β carbon can be attributed to steric elongation of the β-γ bond by an axial substituent, which does not occur in the equatorial form. Elongation of this bond will, according to the theory of Lichtman and Grant (85) produce an upfield shift at the β-carbon.

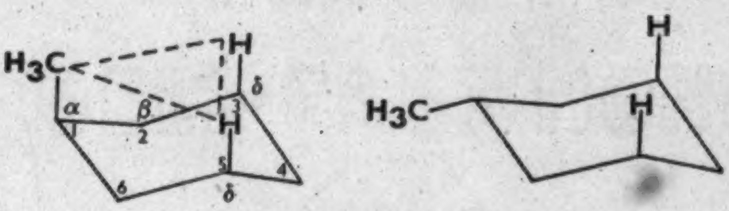


Fig. 12: A comparison of the non-bonded interactions in axially and equatorially substituted methylcyclohexane.

Recently, oxygenated cycloalkane derivatives have received most of the attention with the major effort directed toward the cyclohexanols. Complete results have been presented (86-88), the most extensive set being that of Roberts et al. (86) which are shown in Table 7. It is noted that for each pair of isomers, the ring carbons consistently absorb at higher field in the epimer having the axial hydroxyl function. The upfield shift of ~ 5 ppm for the C-3 and C-5 nuclei in the axial isomers is readily ascribed to the steric perturbation effect already discussed

TABLE 7

Alkyl carbon shieldings of some alkylcyclohexanols

	Chemical shifts (ppm) from TMS						
Substituent*	C-1	C-2	C-3	C-4	C-5	C-6	CH_3
Nil	69.8	35.8	24.7	26.2	24.7	35.8	—
trans-2-methyl	76.9	40.0	34.3	26.1	25.7	35.4	19.1
cis-2-methyl	71.4	36.1	29.6	24.5	21.8	32.1	16.5
cis-3-methyl	70.8	44.3	32.0	35.1	24.7	34.7	22.8
trans-3-methyl	66.8	41.5	26.9	34.7	20.5	33.1	20.5
trans-4-methyl	70.0	33.4	35.1	31.7	35.1	33.4	22.0
cis-4-methyl	66.2	31.7	29.0	30.9	29.0	31.7	21.2

* The first entry in each pair has OH equatorial, while the second has OH predominantly axial.

for γ carbons in the methylcyclohexane system. Also, the C-O bond in the axial epimers is *gauche* with respect to the C-2 to C-3 and C-5 to C-6 bonds, resulting in the observed shielding effect at the carbinyl carbon.

A more quantitative comparison of the data for the alkylcyclohexanols is revealed in Table 8, where the substituent effects of the hydroxyl group are estimated by comparison with the shielding values for the corresponding alkylcyclohexanes (86). The compounds with equatorial hydroxyls form the first group; these data exhibit a marked consistency except for *trans*-2-methylcyclohexanol, for which the carbinyl and methyl carbons are more shielded than in the others. A similar trend is found for *cis*-2-methylcyclohexanol in the second group, in which the hydroxyl function is mainly axial. In both isomers, the hydroxyl and methyl groups are *gauche* and the upfield shift of ~4 ppm found for the methyl carbon relative to its shielding in the corresponding 3- and 4-methyl isomers may be attributed to the γ effect associated with *gauche* forms, as can the enhanced shielding of the carbinyl carbon in the 2-methyl derivatives.

From the results for simple substituted cyclohexanes discussed above, it follows that carbon-13 examinations of carbohydrates will assist both configurational and conformational assignments of sugar molecules. These

TABLE 8

Substituent effects of the hydroxyl group in alkylcyclohexanols

	Chemical shifts (ppm)*						
Substituent*	C-1	C-2	C-3	C-4	C-5	C-6	CH_3
trans-2-methyl	41.0	6.5	-1.5	-1.0	-1.3	8.3	-4.1
cis-3-methyl	43.7	8.1	-1.5	-1.1	-1.4	7.7	-0.4
trans-4-methyl	43.0	8.0	-1.1	-1.8	-1.1	6.3	-1.2
cis-2-methyl	35.2	2.6	-6.6	-2.6	-5.2	5.0	-6.2
trans-3-methyl	39.7	5.3	-6.6	-1.5	-7.1	6.1	-2.7
cis-4-methyl	38.9	4.6	-7.2	-2.6	-7.2	4.6	-2.0

* The shifts reported are for $\Delta\delta = (\delta\ C^{RC_6H_{10}OH} - \delta\ C^{RC_6H_{11}})$ for the corresponding carbons relative to the OH group

expectations have been confirmed by investigations of several monosaccharides and their methyl glycosides (89-93), as well as of four inositols which serve as excellent models for the former (94).

Recently, the application of ^{13}C-n.m.r. for configurational and conformational assignments of the glycosidic linkage in disaccharides has been discussed by Dorman and Roberts (95). Their experimentally determined values for the chemical shifts of nuclei in methyl β-D-cellobioside, β-D-lactoside, and β-D-maltoside, corrected to reference from external TMS are shown in Table 9. In those cases where the two monomeric units were linked through β-glycosidic bonds, the authors assumed that the resonances of C-1', -2', -3, -4, -5, and -6 would be effectively unchanged from their positions in the carbon-13 spectra of their free monomers. The basis of this assumption is the absence of any significant intramolecular steric interactions between the substitutents at these carbons, regardless of the torsion angles around the glycosidic linkage. Indeed, the similarities between the spectra of methyl β-D-cellobioside and β-D-lactoside and their monomer units were quite striking. This was even true of the resonances for C-2, -3' -5' and -6', and although steric interactions between these sites might be expected to be rather severe, the chemical shift differences between the disaccharides and their monomer units were not large. It was thus

TABLE 9

CMR chemical shifts of the methyl β-glycosides of D-cellobiose, D-lactose and D-maltose

	Chemical shifts (ppm) relative to TMS											
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
A*	103.7	74.3	77.0	70.7	76.9	61.9	104.2	74.0	75.7	80.1	75.5	61.4
B†	104.1	72.1	73.9	69.8	76.4	62.1	104.1	73.9	75.8	79.8	75.6	61.4
C††	100.8	74.1	74.1	70.6	72.9	61.9	104.1	73.8	75.7	78.6	77.3	61.7

* Me β-Cellobioside
† Me β-Lactoside
†† Me β-Maltoside

concluded that the conformations of methyl β-D-cellobioside and β-D-lactoside did not involve forms permitting strong intramolecular steric interactions between the two sugar rings.

In their consideration of the spectra of methyl β-D-maltoside, the authors recognized the possibility of steric interactions between the glucopyranose moiety and substituents at C-3' and C-5'. Therefore, it was not possible to assume that the C-3' and C-5' resonances would be unchanged from their positions in their monosaccharide analogs. A comparison of the C-6' resonance in methyl β-maltoside with the C-6 resonance in methyl β-D-glucopyranoside showed very little difference. Intramolecular steric interactions in methyl β-D-maltoside might have been expected to shield this resonance, but these must be small. The chemical shift of C-5' was thus assigned on the assumption that this carbon nucleus would suffer steric perturbations similar to C-6', which was noted to show only small interactions. The assigned resonances for C-2 and C-3' in methyl β-D-maltoside showed a downfield and an upfield shift respectively, when compared to the resonances observed in the monomer sugar units. The authors suggested that in aqueous solution the conformation of methyl β-D-maltoside equilibrated between that predicted by X-ray analysis and a conformation in which rotation of the ether linkages brought C-3' into close proximity with C-2. It is noted however, that these assignments were made only with some difficulty and therefore the explanations above are only tentative.

II. EXPERIMENTAL

A. Materials

1. Solvents and their purification.

i. Dichloromethane.

Reagent grade dichloromethane was shaken with portions of concentrated sulphuric acid until the acid layer remained colourless. It was then washed successively with water and 5% aqueous sodium bicarbonate solution. After drying over anhydrous calcium sulphate, the solvent was distilled from anhydrous calcium sulphate and stored over molecular sieve (96).

ii. Pyridine.

Reagent grade pyridine was dried by storage over molecular sieve.

iii. Chloroform.

Reagent grade chloroform was purified immediately before use by passage down a column of Woelm neutral aluminum oxide. (Waters Associates Inc., Framingham, Mass.) (96).

iv. N,N-Dimethylformamide (DMF).

Reagent grade DMF was dried by storage over molecular sieves.

2. Absorbents for chromatography.

i. Silica gel G.

Silica gel G used for thin layer chromatography was supplied by E. Merck A. G., Darmstadt, W. Germany.

ii. Silicic acid for column chromatography.

Silicar CC-7, 100-200 mesh, was supplied by Mallinckrodt Chemical Works, St. Louis, Mo.

iii. Dowex ion-exchange resin for column chromatography.

Dowex 1-X2 (200-400 mesh, Cl$^-$ form) was supplied by Sigma Chemical Co., St. Louis, Mo. The OH$^-$ form was prepared by passing a liter of a 10% sodium hydroxide solution through a column of ion-exchange resin (600 g, Cl$^-$ form) and washing with distilled water until the eluent was neutral.

3. Reagents.

i. Hydrogenation catalyst.

Palladium-on-charcoal (5%) was supplied by Matheson Coleman and Bell, Norwood, Ohio.

ii. 4-Toluenesulphonyl chloride.

This reagent was supplied by Raylo Chemicals, Edmonton, Alta., and was purified before use by recrystallization from Skellysolve B.

iii. 7-Oxabicyclo[4.1.0]heptane (cyclohexene oxide).

This reagent was supplied by Aldrich Chemical Co., Milwaukee, Wis., and used without further purification.

iv. 2,6-Dimethylcyclohexanone.

2,6-Dimethylcyclohexanone as a mixture of isomers was supplied by Aldrich Chemical Co., Milwaukee, Wis., and used without separation of the isomers.

v. Penta-*O*-acetyl-α- and-β-D-glucopyranoside.

This reagent was supplied by Raylo Chemicals, Edmonton, Alta., and was purified before use by recrystallization from 95% ethanol.

vi. Cyclohexanol.

This reagent was supplied by Aldrich Chemical Co., Milwaukee, Wis., and used without further purification.

vii. *trans*-2-Methylcyclohexanol.

This reagent was supplied by Chemical Samples Co., Columbus, Ohio, and used without further purification.

viii. *trans*-1,2-Cyclohexanediol.

This reagent was supplied by Aldrich Chemical Co., Milwaukee, Wis., and used without further purification.

B. Methods

1. Spectroscopic measurements.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-60, A-56/60A and a HA100 spectrometer in the solvents noted in the text. Chemical shifts are reported in tau (τ) values from tetramethylsilane (TMS).

Proton noise-decoupled carbon-13 natural abundance nuclear magnetic resonance (c.m.r.) spectra, in 0.5 M deuterium oxide (D_2O), were recorded using a Bruker HFX-90 spectrometer with a Nicolet Fourier transform system or a Varian HA100 spectrometer with a Digilab Fourier transform system. Chemical shifts are reported in ppm from TMS as an external standard.

Infrared (i.r.) spectra were recorded on a Perkin-Elmer grating spectrometer (Model 421), at ambient temperature, using matched sodium chloride cells.

All spectra were determined by the spectral services of this department.

2. Chromatography.

Thin layer chromatography (t.l.c.) was performed on Silica Gel G. using microscope slides. The developing solvents for acetylated glucopyranosides were either ether/Skellysolve B (4/1) or benzene/ethyl acetate (2/1). The upper phase of an ethyl acetate/dioxane/water (2/2/1) system was employed for unprotected glucopyranosides. The compounds were visualized by spraying with 5% sulphuric acid in ethanol and heating on a hot plate.

Column chromatography was carried out using silicic acid (100-200 mesh) in the ratio of 30 g/g of compound at a flow rate of 1 ml per min. The developing solvents for individual compounds are specified in the text.

The separation of the diastereoisomeric substituted *trans*-2'-cyclohexyl β-D-glucopyranosides in Sections III-C-6, III-C-9 and III-C-12 on ion-exchange resin (Dowex 1-X2, 200-400 mesh, OH^- form) was achieved on a 1 1/4" x 6' column with a flow rate of 1 ml per min using distilled water as the developing solvent. The appropriate tubes were then evaporated and examined for purity by optical rotation.

3. Distillation.

The routine removal of organic solvents, previously dried over anhydrous sodium sulphate, where necessary, was carried out *in vacuo* (water aspiration, 10-20 mm) at 30-45° using a rotary evaporator.

Fractional distillation was performed using a Vigreux column at reduced pressure under a nitrogen atmosphere.

4. Melting points.

All melting points were determined in capillary tubes using a Gallenkamp melting point apparatus and are uncorrected.

5. Elemental analysis.

Elemental analyses were performed in this department by Mrs. D. Mahlow and Mrs. A. Dunn.

6. Optical activity measurements.

All optical rotations were measured with a Perkin-Elmer polarimeter (Model 141) at the sodium D-line (5892Å), using a 10 cm polarimeter tube. The same tube, with a sample chamber of approximately 1 ml, was used throughout the investigations. The instrument was periodically checked for accuracy with a standard solution of sucrose (c, 1.0 in water).

The solid compounds were weighed directly into tared and calibrated volumetric flasks of 2 ml, previously dried under anhydrous conditions.

Optical rotations for the individual solutions were measured at ambient temperatures (22-24°). The molecular rotations were determined as follows:

$$[M]_D^t = \frac{[\alpha]_D^t \times \text{M.W.}}{100} = \frac{\alpha_D^t \times \text{M.W.}}{C_{25} \times 100}$$

$[M]_D^t$ ≡ molecular rotation of the compound at t °C, recorded at 5892 Å

$[\alpha]_D^t$ ≡ specific rotation of the compound, at t °C

α_D^t ≡ direct angular rotation of the solution of the compound, at t °C

C_{25} ≡ concentration of the compound in g/100 ml of solution at 25° C.

7. Koenigs-Knorr glycosidations. Preparation of tetra-*O*-acetyl-β-D-glucopyranosides (97).

A suspension of ground calcium sulphate (20 g), yellow mercuric oxide (8.92 g, 41 mmoles), mercuric bromide (0.68 g, 1.9 mmoles), dry methylene chloride (200 ml) and the appropriate alcohol (193 mmoles) was stirred for 0.5 h under anhydrous conditions. Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (20 g, 48.2 mmoles) was then added and the stirring continued for 6 h after which time the mixture was filtered through Celite and concentrated *in vacuo* to an oil which was again dissolved in methylene chloride and filtered. The filtrate was again concentrated *in vacuo* to an oil. All tetra-*O*-acetyl-β-D-glucopyranosides prepared by this method were crystallized from 95% ethanol unless otherwise noted.

8. Deacetylations.

All *O*-acetyl-D-glucopyranosides, unless specified, were deacetylated using aqueous methanol and a 5% amount of triethylamine (at pH 11-12) for 10 h at 5°. The resulting foam after evaporation of the methanol solution was dissolved and evaporated sequentially with methanol and absolute ethanol and dried *in vacuo* over P_2O_5. Crystallization solvents are noted in the text.

9. Acetylations.

All α- and β-D-glucopyranosides (4 mmoles) were acetylated with acetic anhydride (48 mmoles) in pyridine (25 ml) for 10 h at 5°. The reaction mixture was then poured into ice-water (100 ml) and left at room temperature for several hours from which the *O*-acetylated compounds crystallized. The crystals were removed by filtration, washed with water, and dried *in vacuo* over P_2O_5.

10. Pascu anomerizations (98).

Titanium tetrachloride (0.9 g, 2.6 mmoles) in absolute chloroform (15 ml) was added to the appropriate *O*-acetyl-β-D-glucopyranoside (4.7 mmoles) in the same solvent (20 ml) at room temperature by means of a dry syringe. The solution was refluxed under anhydrous conditions (reflux time specified in the text for each individual anomerization) and then cooled to room temperature. The chloroform solution was washed with ice-cold water (3 x 15 ml), sodium bicarbonate solution (3 x 15 ml) and water (2 x 15 ml) and then evaporated to yield a pale yellow oil. The oil was then crystallized from solvents specified in the text.

11. Selective tosylations of hydroxymethyl groups.

A solution of *p*-toluenesulphonyl chloride (3.04 g, 15.9 mmoles) in pyridine (15 ml) was added over a period of 0.5 h to a stirred, ice-cold solution of the appropriate β-D-glucopyranoside (14.5 mmoles) in pyridine (20 ml). After 30 h at room temperature the solution was poured into ice water (200 ml) and then stirred for 1 h. The solution was then extracted with chloroform (3 x 75 ml) and the combined chloroform extracts washed sequentially with dilute hydrochloric acid (2 x 25 ml), water (2 x 50 ml), sodium bicarbonate solution (2 x 50 ml) and water (1 x 50 ml).

Evaporation of the chloroform solution yielded a pale yellow oil which crystallized upon the addition of Skellysolve B.

12. Iodinations.

A solution of the appropriate tri-*O*-acetyl-6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (16 mmoles) and sodium iodide (4.8 g, 32 mmoles) was heated for 20 h at 100° under anhydrous conditions, cooled to room temperature and then concentrated to an oil which was dissolved in methylene chloride (100 ml). The methylene chloride solution was then washed with water (3 x 50 ml) and concentrated to yield a crystalline mass. Recrystallization solvents are specified in the text.

13. Hydrogenations.

A suspension of the appropriate tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside (5 g), 5% palladium-on-carbon (5 g) and triethylamine (10 ml) in ethylacetate (250 ml) was hydrogenated at 60 p.s.i. for 19 h. The suspension was filtered through Celite and the filtrate concentrated to yield a crystalline mass.

14. Criteria for purity.

All compounds were recrystallized to constant melting point and rotation.

The purity of the substituted (1'S)- and (1'R)-*trans*-2'-cyclohexyl β-D-glucopyranosides was ensured by effective chromatographic separation on Dowex ion-exchange resin in the OH^- form.

C. Synthetic Investigations

1. Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (99,100).

Penta-*O*-acetyl-α- and-β-D-glucopyranoside (195 g, 0.5 moles) was added with stirring to a 30% solution of hydrogen bromide in acetic acid (500 ml). After 4.5 h the reaction mixture was diluted with methylene chloride (500 ml) and the resulting solution washed with ice-water (2 x 500 ml). The methylene chloride extract was then washed sequentially with ice-water (1 x 500 ml), saturated sodium bicarbonate solution (2 x 200 ml), water (2 x 200 ml) and then concentrated to yield a yellow oil which crystallized upon the addition of Skellysolve B. Recrystallization from an ether-chloroform-Skellysolve B mixture yielded the desired product (149 g, 70%), m.p. 87-88°, $[\alpha]_D^{24}$ + 197.2° (c, 1 in chloroform). [Lit. (101), m.p. 88-89°, $[\alpha]_D^{20}$ + 197.8° (c, 2 in chloroform)].

2. *trans-trans*-2,6-Dimethylcyclohexanol.

Sodium metal (9.5 g, 0.297 g/atoms) was added with cooling to a stirred mixture of 2,6-dimethylcyclohexanone (25 g, 0.198 moles), ether (250 ml) and water (50 ml) at such a rate as to maintain the temperature below 30°. On completion of the reaction, the ethereal layer was separated, washed with dilute hydrochloric acid (2 x 50 ml), water (2 x 50 ml) and distilled at atmospheric pressure using a Vigreuz column to yield a crude product (18 g). T.l.c. using ether/Skellysolve B (1/2) as the developing solvent indicated the presence of two compounds. Chromatography of this mixture on silicic acid using ether/Skellysolve B (1/1) as the developing solvent yielded the title compound (15 g, 59%), m.p. 51-52°. [Lit. (102), m.p. 52°].

Anal. Calc'd. for $C_8H_{16}O$: C, 74.94; H, 12.58.

Found: C: 75.02; H, 12.65

P.m.r. data in chloroform-d: τ 7.32 (triplet, axial hydrogen at C-1, spacing 8 Hz); 7.93 (singlet, OH); 8.0-9.2 (remaining 14 protons).

3. *trans*-2-Chlorocyclohexanol (103).

A solution of cyclohexene oxide (50 g, 0.51 moles) in carbon tetrachloride (50 ml) was cooled to 0° under anhydrous conditions and an atmosphere of nitrogen. Anhydrous hydrochloric acid was then passed through the solution until a saturated solution was obtained. After 1 h, the carbon tetrachloride solution was washed sequentially with water (3 x 50 ml), saturated sodium carbonate solution (2 x 50 ml), water (2 x 50 ml) and concentrated to afford an oil (53 g). Distillation at reduced pressure (water aspiration) yielded (49 g, 72%), b.p. 80.5-81° (13 mm). (Lit. (103), b.p. 70-71° (7 mm); (104), b.p. 77-80° (10 mm); (105), b.p. 71° (7 mm); (106), b.p. 71.2-72.5° (10 mm)].

I.r. data in carbon disulphide was the same as that reported (107).

4. Cyclohexyl β-D-glucopyranoside (2).

i. Cyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (1)

The Koenigs-Knorr reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (30 g, 70.2 mmoles) and cyclohexanol (28.1 g, 282 mmoles) yielded compound 1 (22.5 g, 71.4%), m.p. 119-120°, $[\alpha]_D^{24}$ - 22.4°, (c, 1 in chloroform). [Lit. (108), m.p. 120-121°, $[\alpha]_D^{20}$ - 24.0° (c, 5.3 in chloroform)].

Anal. Calc'd. for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.03.

Found: C, 55.64; H, 6.85.

P.m.r. data for 1, in chloroform-d: τ 4.78 (triplet, H-3, spacing 9 Hz); 5.42 (doublet, H-1, spacing 8 Hz); 5.64-5.99 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.72 and 5.91 respectively); 6.23-6.45 (multiplet, H-5 and H-1' of the cyclohexyl ring; when H-6' and H-6 irradiated H-5 collapsed to a doublet, centered 6.35, spacing 9 Hz); 7.94, 7.98, 7.99, 8.01 (4 acetate groups); 8.1-9.0 (10 remaining cyclohexyl ring protons).

ii. Deacetylation.

Compound 1 (15 g, 34.8 mmoles) was deacetylated to yield a crude 2. Crystallization twice from ethyl acetate yielded compound 2 (7.6 g, 83%), m.p. 132-133°, $[\alpha]_D^{24}$ - 39.9° (c, 1.02 in water). [Lit. (108), m.p. 133-135°, $[\alpha]_D^{20}$ - 39.8° (in water)].

Anal. Calc'd. for $C_{12}H_{22}O_6$: C, 54.94; H, 8.46.

Found: C, 54.63; H, 8.42.

P.m.r. data for 2, in deuterium oxide: τ 5.22 (doublet, H-1, spacing 8 Hz); 6.58 (doublet, H-2, spacing 9 Hz by decoupling with H-1). The ^{13}C-n.m.r. parameters are reported in Table 10.

5. Cyclohexyl α-D-glucopyranoside (4).

i. Cyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (3)

Compound 1 (2 g, 4.65 mmoles) was anomerized under reflux conditions for 1.5 h to yield a pale yellow oil (1.8 g). Crystallization from Skellysolve B afforded compound 3 (1.65 g, 82.5%), m.p. 39-40°, $[\alpha]_D^{24}$ + 127.5° (c, 0.985 in chloroform). [Lit. (108), m.p. 40-41°, $[\alpha]_D$ + 122° (c, 2.6 in chloroform)].

Anal. Calc'd. for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.03. Found: C, 55.64; H, 6.96.

P.m.r. data for 3, in chloroform-d: τ 4.41-4.52 (quartet, H-3, centered at 4.52, spacing 9 Hz); 4.78 (doublet, H-1, spacing 4 Hz); 5.00 (triplet, H-4; spacing 9 Hz); 5.14-5.28 (quartet, H-2, centered at 5.21, spacing 4 Hz); 5.74-6.06 (3 protons H-5, H-6' and H-6); 6.32-6.64 (multiplet, H-1', centered at 6.48); 7.96, 7.98, 8.00, 8.02 (4 acetate signals); 8.1-9.0 (10 remaining cyclohexyl ring protons).

ii. Deacetylation.

Compound 3 (1 g, 2.3 mmoles) was deacetylated to yield crude 4 (0.59 g). Crystallization twice from ethyl acetate afforded compound 4 (0.49 g, 80%), m.p. 121-122°,

$[\alpha]_D^{24}$ + 133.2° (c, 1 in 10% methanol-water). [Lit. (98), m.p. 126°, $[\alpha]_D$ + 133.2° (in water)].

Anal. Calc'd. for $C_{12}H_{22}O_6$: C, 54.94; H, 8.46.
Found: C, 54.80; H, 8.34.

P.m.r. data for 4 in deuterium oxide: τ 4.75 (doublet, H-1, spacing 3.5 Hz); 6.28 (doublet, H-2, spacing 9 Hz by decoupling with H-1). The ^{13}C-n.m.r. parameters are reported in Table 10.

6. (1'S)-*trans*-2'-Methylcyclohexyl β-D-glucopyranoside (5) and (1'R)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (6).

i. (1'R, 1'S)-*trans*-2'-methylcyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside.

The Koenigs-Knorr reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (131.2 g, 320 mmoles) and *trans*-2-methylcyclohexanol (146.4 g, 1.28 moles) yielded the diastereoisomeric mixture (93. g, 72.2%) in four crystal crops of differing melting points and rotation.

1. 4.61 g, m.p. 132-134°, $[\alpha]_D^{24}$ + 4.5° (c, 1 in chloroform)
2. 62.6 g, m.p. 108-111°, $[\alpha]_D^{24}$ − 3.0° (c, 1 in chloroform)
3. 4.78 g, m.p. 93-95°, $[\alpha]_D^{24}$ − 25.7° (c, 1 in chloroform)
4. 21.98 g, m.p. 92-94°, $[\alpha]_D^{24}$ − 28.0° (c, 1 in chloroform).

ii. Deacetylation.

(1'R, 1'S)-*trans*-2'-Methylcyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (48 g, 108 mmoles), $[\alpha]_D^{24}$ - 3.0° (c, 1 in chloroform), was deacetylated and crystallized from ethyl acetate to afford the mixture (1'R, 1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (26.8 g, 90%), m.p. 161-164°, $[\alpha]_D^{24}$ - 20.2° (c, 1 in water).

iii. Chromatographic separation.

The mixture (5 g) was chromatographed using Dowex ion-exchange resin as described in Section II-B-2. 15 ml fractions were collected and compounds 5 and 6 were eluted in a band from 2560-3010 ml of distilled water.

Fraction 1. 2560-2710 ml. Evaporation yielded compound 5 (1.5 g), m.p. 183-184°, $[\alpha]_D^{24}$ + 10.2° (c, 1 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75.

Found: C, 56.50; H, 8.81.

P.m.r. data for 5, in deuterium oxide: τ 5.26 (doublet, H-1, spacing 8 Hz); 6.56 (doublet, H-2, spacing 9 Hz by decoupling with H-1); 8.75 (doublet, CH_3 in the 2' position of the cyclohexyl ring, spacing 6 Hz). The ^{13}C-n.m.r. parameters are reported in Table 10.

Fraction 2. 2725-2870 ml. Evaporation yielded a mixture of compounds 5 and 6 (1.1 g), $[\alpha]_D^{24}$ + 5.2 to -61.2° (c, 1 in water).

Fraction 3. 2885-3010. Evaporation yielded compound 6 (1.7 g) m.p. 145-146° $[\alpha]_D^{24}$ - 72.2° (c, 1 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75.

Found: C, 56.24; H, 8.90.

P.m.r. data for 6, in deuterium oxide: τ 5.42 (doublet, H-1, spacing 8 Hz); 8.99 (doublet, CH_3 in the 2' position of the cyclohexyl ring, spacing 6 Hz). The ^{13}C-n.m.r. parameters are reported in Table 10.

7. (1'S)-*trans*-2'-Methylcyclohexyl α-D-glucopyranoside (9).

i. (1'S)-*trans*-2'-Methylcyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (7).

Compound 5 (1 g, 3.6 mmoles) was acetylated to afford compound 7 (1.56 g, 97%), m.p. 135-136°, $[\alpha]_D^{24}$ + 7.2° (c, 1 in chloroform).

Anal. Calc'd. for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26.

Found: C, 56.73; H, 7.29.

P.m.r. data for 7, in chloroform-d: τ 4.79 (triplet, H-3, spacing 9 Hz); 5.44 (doublet, H-1, spacing

8 Hz); 5.64-6.00 (2 protons as the AB part of an ABX system, H-6' and H-6. When H-5 was irradiated, H-6', H-6 collapsed to an AB quartet centered at 5.64 and 5.93 respectively); 6.19-6.43 (multiplet, H-5, centered at 6.31); 6.82-7.14 (multiplet, H-1' of the cyclohexyl ring, centered at 6.98); 7.96, 7.99, 8.02 (4 acetate signals in the ratio 1:2:1 respectively); 8.1-9.2 (9 remaining cyclohexyl ring protons and a doublet, CH_3 in the 2'position of the cyclohexyl ring, centered at 9.1, spacing 6 Hz).

ii. (1'S)-*trans*-2'-Methylcyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (8).

Compound 7 (1.2 g, 2.7 mmoles) was anomerized under reflux conditions for 1.5 h to yield a pale yellow oil. Crystallization from Skellysolve B afforded compound 8 (1.1 g, 91.7%), m.p. 111-112°, $[\alpha]_D^{24}$ + 153.7° (c, 0.995 in chloroform).

Anal. Calc'd. for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26.

Found: C, 56.60; H, 7.11.

P.m.r. data for 8, in chloroform-d: τ 4.53 (triplet, H-3, spacing of 9 Hz); 4.77 (doublet, H-1, spacing of 4 Hz); 4.98 (triplet, H-4, spacing 9 Hz); 5.12-5.26 (quartet, H-2, centered at 5.19, outside spacings 4 Hz); 5.65-6.02 (3 protons, H-5, H-6' and H-6); 6.72-7.04 (multiplet, H-1' of the cyclohexyl ring, centered at 6.88);

7.93, 7.97, 8.00 (4 acetate signals in the ratio 1:2:1 respectively); 8.1-9.1 (9 remaining cyclohexyl ring protons and a doublet, CH_3 in the 2' position of the cyclohexyl ring, centered 8.99, spacing 6 Hz).

iii. Deacetylation.

Compound (8) (0.75 g, 1.7 mmoles) was deacetylated to yield crude 9 (0.456 g), $[\alpha]^{24}_{D}$ + 160.4° (c, 1 in water). Crystallization twice from ethyl acetate afforded compound 9 (0.35 g, 75%), m.p. 140-141°, $[\alpha]^{24}_{D}$ + 172.4° (c, 1 in water).

Anal. Calc'd for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75.

Found: C, 56.51; H, 8.75.

P.m.r. data for 9, in deuterium oxide: τ 4.97 (doublet, H-1, spacing 3.5 Hz); 6.56 (doublet, H-2, spacing of 9 Hz by decoupling with H-1); 9.08 (doublet, CH_3 in the 2' position of the cyclohexyl ring, spacing 6 Hz). The ^{13}C-n.m.r. parameters are reported in Table 10.

8. (1'R)-*trans*-2'-Methylcyclohexyl α-D-glucopyranoside (12).

i. (1'R)-*trans*-2'-Methylclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (10).

Compound 6 (1 g, 3.6 mmoles) was acetylated to afford compound 10 (1.56 g, 97%), m.p. 101-102°, $[\alpha]^{24}_{D}$ - 45.6° (c, 1 in chloroform).

Anal. Calc'd. for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26.

Found: C, 56.92; H, 7.36.

P.m.r. data for 10, in chloroform-d: τ 4.78 (triplet, H-3, spacing 8.5 Hz); 5.45 (doublet, H-1, spacing 8 Hz); 5.65-5.97 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.73 and 5.89 respectively); 6.24-6.45 (multiplet, H-5, centered at 6.35), 6.73-7.03 (multiplet, H-1' of the cyclohexyl ring, centered at 6.88); 7.94, 7.98, 8.01 (4 acetate signals in the ratio 1:2:1 respectively); 8.1-9.2 (9 remaining cyclohexyl ring protons and a doublet, CH_3 in the 2' position of the cyclohexyl ring, centered at 9.05, spacing 6 Hz).

ii. (1'R)-*trans*-2'-Methylcyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (11).

Compound 10 (1.2 g, 2.7 mmoles) was anomerized under reflux conditions for 1.5 h to yield a pale yellow oil. Crystallization from Skellysolve B afforded compound (11) (1.05 g, 88%), m.p. 59-60°, $[\alpha]_D^{24}$ + 90.7° (c, 1 in chloroform).

Anal. Calc'd. for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26.

Found: C, 56.49; H, 7.40.

P.m.r. data for 11, in chloroform-d: τ 4.50 (triplet, H-3, spacing 9 Hz); 4.84 (doublet, H-1, spacing

4 Hz); 4.98 (triplet, H-4, spacing 9 Hz); 5.07-5.25 (quartet, H-2, centered at 5.16, outside spacing 4 Hz); 5.60-6.05 (3 protons, H-5, H-6' and H-6); 6.84-7.14 (multiplet, H-1' of the cyclohexyl ring, centered 6.99); 7.95, 7.98, 8.01 (4 acetate signals in the ratio 1:2:1 respectively); 8.1-9.1 (9 remaining cyclohexyl ring protons and a doublet, CH_3 in the 2' position of the cyclohexyl ring, centered 9.07, spacing 6 Hz).

iii. Deacetylation.

Compound 11 (0.75 g, 1.7 mmoles) was deaceylated to yield crude 12 (0.451 g), $[\alpha]_D^{24}$ + 82.8° (c, 1.002 in water). Crystallization twice from ethyl acetate yielded compound 12 (0.36 g, 77%), m.p. 160-161°, $[\alpha]_D^{24}$ + 94.2°(c, 1 in water).

Anal. Calc'd. for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75.

Found: C, 56.73; H, 8.91.

P.m.r. data for 12, in 15% methanol-d_4-deuterium oxide: τ 4.94 (doublet, H-1, spacing 3.5 Hz); 6.45 (doublet, H-2, spacing 9Hz by decoupling with H-1); 8.93 (doublet, CH_3 in the 2' position of the cyclohexyl ring, spacing 6 Hz). The ^{13}C-n.m.r. parameters are reported in Table 10.

9. (1'S)-*trans*-2'-Hydroxycyclohexyl β-D-glucopyranoside (13) and (1'R)-*trans*-2'-Hydrocycyclohexyl β-D-glucopyranoside (14).

i. (1'R, 1'S)-*trans*-2'-Hydroxycyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside.

The Koenigs-Knorr reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (20 g, 48.2 mmoles) and *trans*-1,2-cyclohexanediol (22.4 g, 193 mmoles) yielded the diastereoisomeric mixture (14.3 g, 68%) in two crystal crops of differing melting points and rotation.

1. 10.8 g, m.p. 167-168°, $[\alpha]_D^{24}$ - 13.5° (c, 0.995 in chloroform).
2. 3.5 g, m.p. 156-157°, $[\alpha]_D^{24}$ + 6.90° (c, 0.995 in chloroform).

ii. Deacetylation.

(1'R, 1'S)-*trans*-2'-Hydroxycyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside with $[\alpha]_D^{24}$ - 13.5° (c, 0.995 in chloroform) and $[\alpha]_D^{24}$ + 6.9° (c, 0.995 in chloroform), respectively, were deacetylated separately. Crystallization from ethyl acetate afforded a near quantitative yield of (1'R, 1'S)-*trans*-2'-Hydroxycyclohexyl β-D-glucopyranoside with $[\alpha]_D^{24}$ - 47.8° (c, 1.008 in water) and $[\alpha]_D^{24}$ + 4.6° (c, 0.995 in water), respectively.

ii. Chromatographic separation.

The mixture (5 g), $[\alpha]_D^{24}$ - 47.8° (c, 1.008 in water) was chromatographed using Dowex ion-exchange resin as described in Section II-B-2. 10 ml fractions were collected and compounds 13 and 14 were detected in two fractions from 1700-2200 ml and from 3200-3350 ml of distilled water.

Fraction 1. 1700-2200 ml. Evaporation yielded compound 14 (4.05 g), m.p. 115-116°, $[\alpha]_D^{24}$ - 61.2° (c, 1 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97.

Found: C, 51.93: H, 8.21.

P.m.r. data for 14, in deuterium oxide: τ 5.23 (doublet, H-1, spacing 8 Hz); 6.50 (doublet, H-2, spacing 9 Hz by decoupling with H-1). The ^{13}C-n.m.r. parameters are shown in Table 11.

Fraction 2. 3200-3350 ml. Evaporation yielded compound 13 (0.46 g), m.p. 142-143°, $[\alpha]_D^{24}$ + 9.3° (c, 1 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97.

Found: C, 51.73; H, 8.05.

N.m.r. data for 13, in deuterium oxide: τ 5.14 (doublet, H-1, spacing 8 Hz); 6.51 (doublet, H-2, spacing

9 Hz by decoupling with H-1). The ^{13}C-n.m.r. parameters are reported in Table 11.

In a manner similar to that described, the mixture (2.1 g), $[\alpha]_D^{24}$ + 4.6°(c, 0.995) in water) was chromatographed to yield compound 14 (0.13 g) and compound 13 (1.84 g). Their melting points and rotation were identical to those previously found.

10. (1'S)-*trans*-2'-Hydroxycyclohexyl α-D-glucopyranoside (17).

i. (1'S)-*trans*-2'-Acetoxycyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (15).

Compound 13 (1.2 g, 4.3 mmoles) was acetylated to afford compound 15 (1.85 g, 88%), m.p. 120-121°, $[\alpha]_D^{24}$ - 21.4° (c, 1.005 in chloroform).

Anal. Calc'd. for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60.

Found: C, 54.13; H, 6.40.

P.m.r. data for 15, in chloroform-d: τ 5.33 (doublet, H-1, spacing 8 Hz); 5.66-6.00 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 4.75 and 5.92 respectively); 6.26-6.56 (2 protons, H-5 and H-1', centered at 6.41); 7.94, 7.95, 8.01, 8.03 (5 acetate groups in the ratio 1:1:2:1 respectively); 8.2-9.0 (8 cyclohexyl ring protons).

ii. (1'S)-*trans*-2'-Acetoxycyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (16)

Compound 15 (2 g, 4.1 mmoles) was anomerized under reflux conditions for 13 h to yield a pale yellow oil. Cyrstallization from 95% ethanol yielded compound 16 (1.77 g, 86%), m.p. 156-157°, $[\alpha]_D^{24}$ + 156°(c, 1.008 in chloroform).

Anal. Calc'd. for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60.

Found: C, 54.13; H, 6.76.

P.m.r. data for 16, in chloroform-d: τ 4.50-4.70 (quartet, H-3, centered at 4.60, spacing 9 Hz); 4.81 (doublet, H-1, spacing 4 Hz); 4.99 (triplet, H-4, spacing 9 Hz); 5.16-5.30 (quartet, H-2, centered at 5.23, spacing 4 Hz); 5.72-5.97 (3 protons, H-5, H-6' and H-6); 6.31-6.57 (multiplet, H-1', centered at 6.44); 7.92, 7.96, 8.00, 8.02 (5 acetate groups in the ratio 1:2:1:1 respectively); 8.2-9.0 (8 cyclohexyl ring protons).

iii. Deacetylation.

Compound 16 (0.82 g, 1.7 mmoles) was deacetylated to yield crude 17 (0.44 g), $[\alpha]_D^{24}$ + 159.8° (c, 1 in water). Crystallization twice from ethyl acetate afforded compound 17 (0.35 g, 70%), m.p. 137-138°, $[\alpha]_D^{24}$ + 171.4° (c, 1 in water).

Anal. Calc'd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97.

Found: C, 51.79; H, 8.19.

P.m.r. data for 17, in deuterium oxide: τ 4.66 (doublet, H-1, spacing 4 Hz); 6.22 (quartet, H-2, collapsed to doublet, spacing 10 Hz, by decoupling with H-1). The ^{13}C-n.m.r. parameters are reported in Table 11.

11. (1'R)-*trans*-2'-Hydroxycyclohexyl α-D-glucopyranoside (20).

i. (1'R)-*trans*-2'-Acetoxycyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (18).

Compound 14 (1.2 g, 4.3 mmoles) was acetylated to afford compound 18 (1.8 g, 86%), m.p. 140-141°, $[\alpha]_D^{24}$ -29.8° (c, 1 in chloroform).

Anal. Calc'd. for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60.

Found: C, 54.07; H, 6.66.

P.m.r. data for 18, in chloroform-d: τ 4.80 (triplet, H-3, spacing 9 Hz); 5.44 (doublet, H-2, spacing 8 Hz); 5.63-6.00 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.71 and 5.92 respectively); 6.24-6.50 (multiplet, H-5 and H-1', centered at 6.37); 7.94, 7.98, 8.00, 8.02 (5 acetate groups in the ratio 1:2:1:1 respectively); 8.2-9.0 (8 cyclohexyl ring protons).

ii. (1'R)-*trans*-2'-Acetoxycyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (19).

Compound 18 (3 g, 6.1 mmoles) was anomerized under reflux conditions for 13 h. Crystallization from Skellysolve B afforded a mixture of compounds 18 and 19 (2.8 g), $[\alpha]_D^{24}$ + 35.5° (c, 1 in chloroform). The mixture was then separated on a column of silicic acid using ether/Skellysolve B (6/4) as the developing solvent. Recrystallization of 19 (1.31 g) thus obtained from 95% ethanol yielded 1.2 g (40%), m.p. 142-143°, $[\alpha]_D^{24}$ + 88.2° (c, 1 in chloroform).

Anal. Calc'd. for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60.

Found: C, 53.94; H, 6.53.

P.m.r. data for 19, in chloroform-d: τ 4.42 - 4.66 (quartet, H-3, centered at 4.54, spacing 9.5 Hz); 4.68 (doublet, H-1, spacing 4 Hz); 5.00 (triplet, H-4, spacing 9.5 Hz); 5.14-5.28 (quartet, H-2, centered at 5.21, spacing 4 Hz); 5.72-6.02 (3 protons, H-5, H-6' and H-6); 6.24-6.50 (multiplet, H-1', centered at 6.37); 7.93, 7.98, 8.01, 8.02 (5 acetate groups in the ratio 1:2:1:1 respectively); 8.1-9.1 (8 cyclohexyl ring protons).

iii. Deacetylation.

Compound 19 (1 g, 2 mmoles) was deacetylated at room temperature using anhydrous methanol (20 ml) and a catalytic amount of sodium metal at pH 11-12. The reaction mixture was then neutralized with Dowex 50W-X12 (100-200 mesh) acid ion-exchange resin, filtered and evaporated to yield crude, crystalline 19 (0.56 g). Recrystallization twice from ethyl acetate afforded 19 (0.51 g, 86%), m.p. 130-131°, $[\alpha]_D^{24}$ + 93.1° (c, 1.01 in water).

Anal. Calc'd. for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97.

Found: C, 51.53; H, 7.79.

P.m.r. data for 20, in deuterium-oxide: τ 4.75 (doublet, H-1, spacing 4 Hz). The ^{13}C-n.m.r. parameters are shown in Table 11.

12. (1'S)-*trans*-2'-Chlorocyclohexyl β-D-glucopyranoside (21) and (1'R)-*trans*-2'-chlorocyclohexyl β-D-glucopyranoside (22).

i. (1'R, 1'S)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside.

The Koenigs-Knorr reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (20 g, 48.2 mmoles) and *trans*-2-chlorocyclohexanol (25.9 g, 193 mmoles) yielded the diastereoisomeric mixture (13.8 g, 60.8%), m.p. 140-143°, $[\alpha]_D^{24}$ + 0.4° (c, 1.02 in chloroform).

ii. Deacetylation.

(1'R, 1'S)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (10 g, 21.7 mmoles) was deacetylated and crystallized from ethyl acetate to afford a near quantitative yield of (1'R, 1'S)-*trans*-2'-chlorocyclohexyl β-D-glucopyranoside, $[\alpha]_D^{24}$ - 6.0° (c, 1 in water).

iii. Chromatographic separation.

The mixture (5 g) was chromatographed using Dowex ion-exchange resin as described in Section II-B-2. 10 ml fractions were collected and compounds 21 and 22 were detected in two fractions from 1780-2140 ml and from 2180-2520 ml of distilled water.

Fraction 1. 1780-2140 ml. Evaporation yielded compound 21 (2.9 g), m.p. 151-152°, $[\alpha]_D^{24}$ + 9.6° (c, 1.01 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{12}H_{21}O_6Cl$: C, 48.56; H, 7.13; Cl, 11.95.

Found: C, 48.46; H, 6.96; Cl, 12.16.

P.m.r. data for 21, in deuterium oxide: τ 5.02 (doublet, H-1, spacing 7.5 Hz); 6.42 (triplet, H-2, spacing 8 Hz). The ^{13}C-n.m.r. parameters are reported in Table 12.

Fraction 2. 2180-2520 ml. Evaporation yielded compond 22 (1.54 g), m.p. 126.5-127.5°, $[\alpha]_D^{24}$ - 67.1° (c, 1 in water). Recrystallization from ethyl acetate produced no change in melting point or rotation.

Anal. Calc'd. for $C_{12}H_{21}O_6Cl$: C, 48.56; H, 7.13; Cl, 11.95.

Found: C, 48.37; H, 7.00; Cl, 11.83.

P.m.r. data for 22, in deuterium oxide: τ 5.14 (doublet, H-1, spacing 7.5 Hz); 6.46 (triplet, H-2, spacing 8 Hz). The ^{13}C-n.m.r. parameters are shown in Table 12.

13. (1'S)-*trans*-2'-Chlorocyclohexyl α-D-glucopyranoside (25).

i. (1'S)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (23).

Compound 21 (1.5 g, 5.1 mmoles) was acetylated to afford compound 23 (2.2 g, 95%), m.p. 153-154°, $[\alpha]_D^{24}$ + 8.36°(c, 0.993 in chloroform).

Anal. Calc'd. for $C_{20}H_{29}O_{10}Cl$: C, 51.67; H, 6.29; Cl, 7.63.

Found: C, 51.41; H, 6.12; Cl, 7.95.

P.m.r. data for 23, in chloroform-d: τ 4.75 (triplet, H-3, spacing 9 Hz); 5.30 (doublet, H-1, spacing 8 Hz); 5.65-5.98 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.73 and 5.90 respectively); 6.13-6.66 (3 protons, H-5, H-1', H-2'); 7.95, 7.97, 8.00, 8.02 (4 acetate signals); 8.2-9.0 (8 remaining cyclohexyl ring protons).

ii. (1'S)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (24).

Compound 23 (1.5 g, 3.2 mmoles) was anomerized under reflux conditions for 10 h to yield a pale yellow oil. Crystallization twice from Skellysolve B yielded 24 (1.2 g, 80%), m.p. 138-139°, $[\alpha]_D^{24}$ + 149.9° (c, 1.008 in chloroform).

Anal. Calc'd. for $C_{20}H_{29}O_{10}Cl$: C, 51.67; H, 6.29
Cl, 7.63.

Found: C, 51.63; H, 6.23; Cl, 7.87.

P.m.r. data for 24, in chloroform-d: τ 4.51-4.71 (quartet, H-3, centered at 4.61, spacing 9 Hz); 4.88 (doublet, H-1, spacing 4 Hz); 4.95-5.14 (quartet, H-4, centered at 5.05, spacing 9 Hz); 5.23-5.37 (quartet, H-2, centered at 5.30, spacing 4 Hz); 5.52-5.70 (multiplet, H-5, centered at 5.61); 5.76-6.08 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.84 and 6.00 respectively); 6.11-6.68 (2 protons, H-1' and H-2'); 7.93, 7.96, 7.98, 8.00 (4 acetate signals); 8.2-9.0 (8 remaining cyclohexyl ring protons).

iii. Deacetylation.

Compound 24 (0.8 g, 1.7 mmoles) was deacetylated to yield crude 25 (0.54 g), $[\alpha]_D^{24}$ + 158.5° (c, 1 in water). Crystallization twice from ethyl acetate afforded 25 (0.5 g, 87%), m.p. 159-160°, $[\alpha]_D^{24}$ + 160.9° (c, 1.01 in water).

Anal. Calc'd. for $C_{12}H_{21}O_6Cl$: C, 48.57;

H, 7.13; Cl, 11.95.

Found: C, 48.36; H, 7.06; Cl, 11.97.

P.m.r. data for 25, in deuterium oxide: τ 4.96 (doublet, H-1, spacing of 4 Hz). The ^{13}C n.m.r. parameters are reported in Table 12.

14. (1'R)-*trans*-2'-Chlorocyclohexyl α-D-glucopyranoside (28).

i. (1'R)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (26).

Compound 22 (1 g, 3.37 mmoles) was acetylated to afford compound 26 (1.5 g, 96%), m.p. 123-124°, $[\alpha]_D^{24}$ -45.6° (c, 1.01 in chloroform).

Anal. Calc'd. for $C_{20}H_{29}O_{10}Cl$: C, 51.67;

H, 6.29; Cl, 7.63.

Found: C, 51.54; H, 6.23; Cl, 7.46.

P.m.r. data for 26, in chloroform-d: τ 4.76 (triplet, H-3, spacing 8.5 Hz); 4.93 (triplet, H-2, spacing 7.5 Hz); 5.03 (triplet, H-4, spacing 8.5 Hz); 5.44 (doublet, H-1, spacing 7.5 Hz); 5.64-6.06 (3 protons, H-5, and H-6', H-6); 6.18-6.44 (multiplet, H-1' and H-2', centered at 6.31); 7.96, 8.00, 8.02, 8.04 (4 acetate signals); 8.1-9.0 (8 remaining cyclohexyl ring protons).

ii. (1'R)-*trans*-2'-Chlorocyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (27).

Compound 26 (1.3 g, 2.8 mmoles) was anomerized under reflux conditions for 10 h to yield a pale yellow oil. Cyrstallization twice from 95% ethanol afforded compound 27 (1.03 g, 80%), m.p. 46-48°, $[\alpha]_D^{24}$ + 91.1° (c, 1.01 in chloroform).

Anal. Calc'd. for $C_{20}H_{29}O_{10}Cl$: C, 51.67;
H, 6.29; Cl, 7.63.

Found: C, 51.51; H, 6.39; Cl, 7.53.

P.m.r. data for 27, in chloroform-d: τ 4.37-4.57 (quartet, H-3, centered at 4.47, spacing 9 Hz); 4.60 (doublet, H-1, spacing 4 Hz); 4.94 (triplet, H-4, spacing 9 Hz); 5.06-5.21 (quartet, H-2, centered at 5.14, spacing 4 Hz); 5.74-6.06 (5 protons, H-5, H-6' and H-6, H-1' and H-2'); 7.97, 7.98, 7.99, 8.00 (4 acetate signals); 8.1-9.0 (8 remaining cyclohexyl ring protons).

iii. Deacetylation.

Compound 27 (1 g, 2.2 mmoles) was deacetylated to yield crude 28 (0.62 g), $[\alpha]_D^{24}$ + 75.1° (c, 1 in water). Crystallization twice from ethyl acetate afforded compound 28 (0.50 g, 80%), m.p. 151-152°, $[\alpha]_D^{24}$ + 85.2° (c, 1 in water).

Anal. Calc'd. for $C_{12}H_{21}O_6Cl$: C, 48.57;
H, 7.13; Cl, 11.95.

Found: C, 48.70; H, 7.26; Cl, 11.74.

P.m.r. data for 28, in deuterium oxide: τ 4.66 (doublet, H-1, spacing 4 Hz); 6.30-6.44 (quartet, H-2, centered at 6.37, spacing 4 Hz). The ^{13}C-n.m.r. parameters are shown in Table 12.

15. (2'R)-*trans*-(6'S)-*trans*-Dimethylcyclohexyl β-D-glucopyranoside (30).

i. (2'R)-*trans*-(6'S)-*trans*-Dimethylcyclohexyl tetra-*O*-acetyl-β-D-glucopyranoside (29).

The Koenigs-Knorr reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.46 g, 6 mmoles) and *trans-trans*-2,6-dimethylcyclohexanol (3 g, 23.2 mmoles) yielded crude 29 (3.5 g). The crude product was chromatographed on silicic acid using ether/Skellysolve B (6/4) as the developing solvent to yield compound 29 (1.68 g, 60%), m.p. 129-130°, $[\alpha]_D^{24}$ -22.6° (c, 1.01 in chloroform).

Anal. Calc'd. for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47.

Found: C, 57.33; H, 7.77.

P.m.r. data for 29, in chloroform-d: τ 4.78 (triplet, H-3, spacing 9 Hz); 5.44 (doublet, H-1, spacing

8 Hz); 5.72-5.96 (H-6' and H-6); 6.30-6.54 (multiplet, H-5, centered at 6.42); 7.27 (triplet, H-1', spacing 9 Hz); 7.97, 8.00, 8.02, 8.04 (4 acetate signals); 8.20-9.2 (8 remaining cyclohexyl ring protons and two CH_3 doublets).

ii. Deacetylation.

Compound 29 (0.5 g, 1.1 mmoles) was deacetylated to yield crude 30 (0.30 g). Crystallization twice from ethyl acetate afforded compound 30 (0.25 g, 80%), m.p. 173-174°, $[\alpha]_D^{24}$ - 18.1° (c, 1 in water).

Anal. Calc'd. for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03.

Found: C, 57.74; H, 9.15.

P.m.r. data for 30, in deuterium oxide: τ 5.15 (doublet, H-1, spacing 7.5 Hz); 6.64 (triplet, H-1', spacing 9.5 Hz). The ^{13}C-n.m.r. parameters are shown in Table 13.

16. (2'R)-*trans*-(6'S)-*trans*-Dimethylcyclohexyl α-D-glucopyranoside (32).

i. (2'R)-*trans*-(6'S)-*trans*-Dimethylcyclohexyl tetra-*O*-acetyl-α-D-glucopyranoside (31).

Compound 29 (0.52 g, 1.14 mmoles) was anomerized under reflux conditions for 2.5 h to yield a pale yellow oil. Crystallization from 95% ethanol afforded compound 31 (0.46 g, 88%), m.p. 110-111°, $[\alpha]_D^{24}$ + 94.7° (c, 1.01 in chloroform).

Anal. Calc'd. for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47.

Found: C, 57.51; H, 7.38.

P.m.r. data for 31, in chloroform-d: τ 4.35-4.55 (quartet, H-3, centered at 4.45, spacing 9 Hz); 4.80 (doublet, H-1, spacing 4 Hz); 5.00 (triplet, H-4, spacing 9 Hz); 4.93-5.09 (quartet, H-2, centered at 5.01, spacing 4 Hz); 5.66-6.08 (3 protons H-5, H-6' and H-6); 7.17 (triplet, H-1', spacing 9.5 Hz); 7.93, 7.96, 7.97, 8.00 (4 acetate signals); 8.2-9.1 (8 remaining cyclohexyl ring protons and two CH_3 doublets).

ii. Deacetylation.

Compound 31 (0.4 g, 0.7 mmoles) was deacetylated to yield crude 32 (0.24 g). Crystallization from ethyl acetate afforded compound 32 (0.21 g, 84%), m.p. 158-159°, $[\alpha]_D^{24}$ + 119.6°(c, 0.988 in water).

Anal. Calc'd. for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03.

Found: C, 57.68; H, 8.75.

P.m.r. data for 32, in deuterium oxide: τ 4.74 (doublet, H-1, spacing 4 Hz); 6.95 (triplet, H-1', spacing 9 Hz). The ^{13}C-n.m.r. parameters are reported in Table 13.

17. Cyclohexyl 6-deoxy-β-D-glucopyranoside (37).

i. Cyclohexyl 6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (33).

Compound 2 (6.3 g, 24 mmoles) was tosylated in the manner previously described. Recrystallization of the crude product from an ethyl acetate-Skellysolve B mixture afforded compound 33 (8.2 g, 82%), m.p. 119-129°, $[\alpha]_D^{24}$ -38.2° (c, 1.025 in chloroform).

Anal. Calc'd. for $C_{19}H_{28}O_8S$: C, 54.79;
H, 6.78; S, 7.70.
Found: C, 54.75; H, 6.80; S, 7.67.

P.m.r. data for 33, in chloroform-d: τ 2.18 - 2.76 (4 aromatic protons as an AA'BB' quartet centered at 2.47); 7.62 (singlet, CH_3 of the *p*-toluenesulphonyl group).

ii. Cyclohexyl tri-*O*-acetyl-6-*O*-p-toluenesulphonyl-β-D-glucopyranoside (34).

Compound 33 (7.8 g, 19.2 mmoles) was acetylated to afford compound 34 (8.73 g, 86%), m.p. 100-101°, $[\alpha]_D^{24}$ - 13.4° (c, 1 in chloroform).

Anal. Calc'd. for $C_{25}H_{34}O_{11}S$: C, 55.34;
H, 6.32; S, 5.91.
Found: C, 55.05; H, 6.25; S, 6.14.

P.m.r. data for 34, in chloroform-d: τ 2.20 -2.74 (4 aromatic protons as a AA'BB' quartet, centered at 2.47); 4.86 (triplet, H-3, spacing 9 Hz); 5.44 (doublet, H-1, spacing 8 Hz); 5.83-6.06 (H-6' and H-6); 6.20-6.60 (multiplet, H-5 and H-1'); 7.79 (singlet, CH_3 of the *p*-toluenesulphonyl group); 8.02, 8.05, 8.06 (3 acetate signals); 8.2-9.0 (10 remaining cyclohexyl ring protons).

iii. Cyclohexyl tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside (35).

Compound 34 (8.5 g, 15.7 mmoles) was reacted with sodium iodide as previously described to yield a crystalline mass (6.83 g). Recrystallization from 95% ethanol afforded compound 35 (6 g, 77%), m.p. 168-169°, $[\alpha]_D^{24}$ - 5.4° (c, 1.05 in chloroform).

Anal. Calc'd. for $C_{18}H_{27}O_8I$: C, 43.39;
H, 5.46; I, 25.47.

Found: C, 43.35; H, 5.48; I, 25.68.

P.m.r. data for 35, in chloroform-d: τ 4.83 (triplet, H-3, spacing 9 Hz); 5.05 (triplet, H-2, spacing 8 Hz); 5.16 (triplet, H-4, spacing 9 Hz); 5.43 (doublet, H-1, spacing 8 Hz); 6.22-7.04 (4 protons, H-5, H-6' and H-6, H-1'); 7.99, 8.01, 8.04 (3 acetate signals); 8.1-9.0 (10 remaining cyclohexyl ring protons).

iv. Cyclohexyl tri-*O*-acetyl-6-deoxy-β-D-glucopyranoside (36).

Compound 35 (4.86 g, 9.7 mmoles) was hydrogenated at 60 p.s.i to yield a crystalline mass (3.46 g). Recrystallization from 95% ethanol afforded compound 36 (3 g, 83%), m.p. 126-127°, $[\alpha]_D^{24}$ - 18.4° (c, 0.998 in chloroform).

Anal. Calc'd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58.

Found: C, 58.03; H, 7.51.

P.m.r. data for 36, in chloroform-d: τ 4.83 (triplet, H-3, spacing 9 Hz); 4.99-5.16 (quartet, H-2, centered at 5.08, spacing 8 Hz); 5.20 (triplet, H-4, spacing 9 Hz); 5.45 (doublet, H-1, spacing 8 Hz); 6.30-6.62 (2 protons, H-5 and H-1'); 7.98, 8.02 (3 acetate groups in ratio 2:1 respectively); 8.1-9.0 (10 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered at 8.79, spacing 6 Hz)

v. Deacetylation.

Compound 36 (2.3 g, 6.2 mmoles) was deacetylated to yield crude 37 (1.4 g), $[\alpha]_D^{24}$ - 50.2° (c, 1 in 10% methanol-water). Crystallization twice from an acetone-Skellysolve B mixture afforded compound 37 (1.2 g, 79%), m.p. 115-116°, $[\alpha]_D^{24}$ - 55.5° (c, 1.008 in 10% methanol-water).

Anal. Calc'd. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00.

Found: C, 58.60; H, 9.04.

P.m.r. data for 37, in 10% methanol-d_4-deuterium oxide: τ 5.36 (doublet, H-1, spacing 8 Hz); 6.67 (doublet, H-2, spacing 9 Hz by decoupling with H-1); 8.56 (doublet, 6-deoxy CH_3, spacing 6 Hz).

18. Cyclohexyl 6-deoxy-α-D-glucopyranoside (39).

i. Cyclohexyl tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (38).

Compound 36 (2 g, 5.4 mmoles) was anomerized under reflux conditions for 1.5 h to yield an oil which crystallized upon the addition of Skellysolve B (1.9 g), $[\alpha]_D^{24}$ +159.2° (c, 1.005 in chloroform). Recrystallization from 95% ethanol afforded compound 38 (1.5 g, 75%), m.p. 143-144°, $[\alpha]_D^{24}$ + 165.1° (c, 1.018 in chloroform).

Anal. Calc'd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58.

Found: C, 57.86; H, 7.46.

P.m.r. data for 38, in chloroform-d: τ 4.47-4.65 (quartet, H-3, centered 4.56, spacing 9 Hz); 4.87 (doublet, H-1, spacing 3.5 Hz); 5.19-5.33 (quartet, H-2, centered 5.26, spacing 3.5 Hz). 5.25 (triplet, H-4, spacing 9 Hz); 5.87-6.17 (multiplet, H-5, centered 6.02); 6.34-6.62 (multiplet, H-1', centered 6.48); 7.97, 8.01 (3 acetate groups in the ratio 2:1 respectively); 8.0-9.1 (10 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered at 8.85, spacing 6 Hz.

ii. Deacetylation.

Compound 38 (0.9 g, 2.4 mmoles) was deacetylated to yield crude 39 (0.58 g), $[\alpha]_D^{24}$ + 126.4° (c, 1 in 10% methanol-water). Crystallization twice from an acetone-Skellysolve B mixture afforded compound 39 (0.53 g, 89%), m.p. 117-118°, $[\alpha]_D^{24}$ + 128.4° (c, 1 in 10% methanol-water).

Anal. Calc'd. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00.

Found: C, 58.50; H, 9.03.

P.m.r. data for 39, in deuterium oxide: τ 4.91 (doublet, H-1, spacing 3.5 Hz); 8.61 (doublet, 6-deoxy CH_3, spacing 6 Hz).

19. (1'S)-*trans*-2'-Methylcyclohexyl 6-deoxy-β-D-glucopyranoside (44).

i. (1'S)-*trans*-2'-Methylcyclohexyl 6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (40).

Compound 5 (4 g, 14.5 mmoles) was tosylated in the manner previously described. Recrystallization from a ethyl acetate-Skellysolve B mixture and then from a benzene-ethanol mixture afforded compound 40 (5.3 g, 85%), m.p. 127-128°, $[\alpha]_D^{24}$ - 18.2° (c, 1.008 in chloroform).

Anal. Calc'd. for $C_{20}H_{30}O_8S$: C, 55.80;
H, 7.02; S, 7.45.

Found: C, 55.58; H, 6.78; S, 7.18.

P.m.r. data for 40, in chloroform-d: τ 2.20-2.78 (4 aromatic protons as an AA'BB' quartet, centered at 2.40); 7.60 (singlet, CH_3 of *p*-toluenesulphonyl group).

ii. (1'S)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (41).

Compound 40 (5.12 g, 11.9 mmoles) was acetylated to afford crude 41 (6.2 g). Recrystallization from 95% ethanol yielded compound 41 (5.7 g, 86%), m.p. 155-156°, $[\alpha]_D^{24}$ + 5.0° (c, 1 in chloroform).

Anal. Calc'd. for $C_{26}H_{36}O_{11}S$: C, 56.10;
H, 6.52; S, 5.76.

Found: C, 56.00; H, 6.52; S, 5.86.

P.m.r. data for 41, in chloroform-d: τ 2.20-2.72 (4 aromatic protons as an AA'BB' quartet, centered at 2.46); 4.79 (triplet, H-3, spacing 9 Hz); 5.06 (triplet, H-2, spacing 8 Hz); 5.11 (triplet, H-4, spacing 9.5 Hz); 5.45 (doublet, H-1, spacing 8 Hz); 5.76-6.04 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.83 and 5.97 respectively); 6.12-6.34 (multiplet, H-5, centered at 6.23); 6.83-7.12 (multiplet, H-1', centered at 6.98); 7.54 (singlet, CH_3 of the *p*-toluenesulphonyl group); 7.97, 8.01 (3 acetate groups in ratio 2:1 respectively); 8.1-9.2 (9 remaining cyclohexyl ring protons; doublet, CH_3, centered at 9.1, spacing 6 Hz).

iii. (1'S)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside (42).

Compound 41 (5.4 g, 9.8 mmoles) was reacted with sodium iodide as previously described to yield a crystalline mass (4.94 g). Recrystallization from 95% ethanol afforded compound 42 (4.29 g, 85%), m.p. 186-187° $[\alpha]_D^{24}$ + 20.5° (c, 1 in chloroform).

Anal. Calc'd. for $C_{21}H_{29}O_8I$: C, 44.54;
H, 5.71; I, 24.77.

Found: C, 44.72; H, 5.79; I, 24.78.

P.m.r. data for 42, in chloroform-d: τ 4.84 (triplet, H-3, spacing 9 Hz); 5.04 (quartet, H-2, spacing 8 Hz); 5.20 (triplet, H-4, spacing 9 Hz); 5.46 (doublet, H-1, spacing 8 Hz); 6.36-7.08 (4 protons, H-5, H-6' and H-6, H-1'); 7.96, 7.98, 8.00 (3 acetate groups), 8.1-9.2 (9 remaining cyclohexyl ring protons; doublet, CH_3, centered at 9.09, spacing 6 Hz).

iv. (1'S)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-β-D-glucopyranoside (43).

Compound 42 (4.14 g, 8.1 mmoles) was hydrogenated at 60 p.s.i. to yield a crystalline mass (3.06 g). Recrystallization from 95% ethanol afforded compound 43 (2.6 g, 83%), m.p. 142-143°, $[\alpha]_D^{24}$ + 13.4° (c, 1 in chloroform).

Anal. Calc'd. for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83.

Found: C, 58.83; H, 7.83.

P.m.r. data for 43, in chloroform-d: τ4.84 (triplet, H-3, spacing 9 Hz); 5.11 (triplet, H-2, spacing 8 Hz); 5.20 (triplet, H-4, spacing 9 Hz); 5.44 (doublet, H-1, spacing 8 Hz); 6.31-6.59 (multiplet, H-5, centered at 6.45); 7.82-8.12 (multiplet, H-1', centered at 6.97); 7.94, 7.96, 7.98 (3 acetate groups), 8.1-9.2 (9 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered at 8.76, spacing 6 Hz; doublet, CH_3, centered at 9.06, spacing 6 Hz).

v. Deacetylation.

Compound 43 (1 g, 2.85 mmoles) was deacetylated to yield crude 44 (0.65 g), $[\alpha]_D^{24}$ - 2.2° (c, 1.005 in chloroform). Crystallization twice from an ethyl acetate-Skellysolve B mixture afforded compound 44 (0.54 g, 81%), m.p. 133-134°, $[\alpha]_D^{24}$ - 1.7° (c, 0.995 in 10% methanol-water).

Anal. Calc'd. for $C_{13}H_{24}O_5$: C, 59.98; H,9.29.

Found: C, 59.60; H, 9.11.

P.m.r. data for 44, in 15% methanol-d_4-deuterium oxide: τ 5.49 (doublet, H-1, spacing 8 Hz); 6.68 (doublet, H-2, spacing 8 Hz by decoupling with H-1); 8.66 (doublet, 6-deoxy CH_3, spacing 6 Hz); 8.99 (doublet, CH_3, spacing 6 Hz).

20. (1'S)-*trans*-2'-Methylcyclohexyl 6-deoxy-α-D-glucopyranoside (46).

i. (1'S)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (45)

Compound 43 (1.36 g, 3.5 mmoles) was anomerized under reflux conditions for 1.5 h to yield an oil which cyrstallized upon the addition of Skellysolve B (1.2 g), $[\alpha]_D^{24}$ + 162.6° (c, 1.005 in chloroform). Recrystallization twice from Skellysolve B afforded compound 45 (1.04 g, 76%), m.p. 94-95°, $[\alpha]_D^{24}$ + 175.3° (c, 1 in chloroform).

Anal. Calc'd. for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83.

Found: C, 59.29; H, 7.74.

P.m.r. data for 45, in chloroform-d: τ 4.41-4.61 (quartet, H-3, centered at 4.51, spacing 9 Hz); 4.79 (doublet, H-1, spacing 4 Hz); 5.09-5.23 (quartet, H-2, centered at 5.16, spacing 4 Hz); 5.17 (triplet, H-4, spacing

9 Hz); 5.69-6.03 (multiplet, H-5, centered at 5.86); 6.72-7.06 (multiplet, H-1', centered at 6.89); 7.94, 7.98 (3 acetate groups in the ratio 2:1 respectively); 8.0-9.1 (9 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered at 8.83, spacing 6 Hz; doublet, CH_3, centered at 8.97, spacing 6 Hz).

ii. Deacetylation.

Compound 45 (0.7 g, 1.8 mmoles) was deacetylated to yield crude 46 (0.49 g), $[\alpha]_D^{24}$ + 165.2° (c, 1 in 10% methanol-water). Crystallization twice from an acetone-Skellysolve B mixture afforded compound 46 (0.35 g, 81%), m.p. 119-120°, $[\alpha]_D^{24}$ + 170.2° (c, 1 in 10% methanol-water).

Anal. Calc'd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29.

Found: C, 59.66; H, 9.20.

P.m.r. data for 46, in 15% methanol-d_4-deuterium oxide: τ 5.20 (doublet, H-1, spacing 3.5 Hz); 6.69 (doublet, H-2, spacing 9 Hz by decoupling with H-1); 8.92 (doublet, 6-deoxy CH_3, spacing 6 Hz); 9.17 (doublet, CH_3, spacing 6 Hz).

21. (1'R)*trans*-2'-Methylcyclohexyl 6-deoxy-β-D-glucopyranoside (51).

i. (1'R)-*trans*-2'-Methylcyclohexyl 6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (47).

Compound 6 (4 g, 14.5 mmoles) was tosylated in the manner previously described. Recrystallization of the crude product from an ethyl acetate-Skellysovle B mixture and then from benzene afforded compound 47 (4.85 g, 78%), m.p. 124-125° $[\alpha]_D^{24}$ - 57.2° (c, 1.005 in chloroform).

Anal. Calc'd. for $C_{20}H_{30}O_8S$: C, 55.89; H, 7.02; S, 7.45.

Found: C, 55.53; H, 7.08; S, 7.30.

P.m.r. data for 47, in chloroform-d: τ 2.22-2.78 (4 aromatic protons as an AA'BB' quartet, centered at 2.50); 7.60 (singlet, CH_3 of the *p*-toluenesulphonyl group); 9.13 (doublet, CH_3, spacing 6 Hz).

ii. (1'R)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-*O*-*p*-toluenesulphonyl-β-D-glucopyranoside (48).

Compound 47 (4.6 g, 10.6 mmoles) was acetylated to afford crude 48 (5.72). Recrystallization from 95% ethanol afforded compound 48 (4.94 g, 83%), m.p. 130-131°, $[\alpha]_D^{24}$ - 29.2° (c, 1 in chloroform).

Anal. Calc'd. for $C_{26}H_{36}O_{11}S$: C, 56.10;

H, 6.52; S, 5.76.

Found: C, 56.02; H, 6.64; S, 5.79.

P.m.r. data for 48, in chloroform-d: τ 2.18-2.70 (4 aromatic protons as an AA'BB' quartet, centered at 2.44); 4.78 (triplet, H-3, spacing 9 Hz); 5.08 (triplet, H-4, spacing 9 Hz); 5.11 (triplet, H-2, spacing 8 Hz); 5.45 (doublet, H-1, spacing 8 Hz); 5.80-6.05 (2 protons as the AB part of an ABX system, H-6' and H-6, centered at 5.79 and 5.98 respectively); 6.14-6.36 (multiplet, H-5, centered at 6.25); 6.73-7.00 (multiplet, H-1', centered at 6.87); 7.54 (singlet, CH_3 of the *p*-toluenesulphonyl group); 7.96, 8.00 (3 acetate groups in the ratio 2:1 respectively); 8.1-9.2 (9 remaining cyclohexyl ring protons; doublet, CH_3, centered at 9.07, spacing 6 Hz).

iii. (1'R)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside (49).

Compound 48 (4.75 g, 8.35 mmoles) was reacted with sodium iodide as previously described to yield a crystalline mass (4.3 g). Recrystallization from 95% ethanol afforded compound 49 (3.72 g, 85%), m.p. 194-195°, $[\alpha]_D^{24}$ - 25.9° (c, 1.005 in chloroform).

Anal. Calc'd. for $C_{21}H_{29}O_8I$: C, 44.54;
H, 5.71; I, 24.77.

Found: C, 44.72; H, 5.94; I, 24.92.

P.m.r. data for 49, in chloroform-d: τ 4.80 (triplet, H-3, spacing 9 Hz); 5.07 (quartet, H-2, spacing 8 Hz); 5.14 (triplet, H-4, spacing 9 Hz); 5.44 (doublet, H-1, spacing 8 Hz); 6.34-7.00 (4 protons, H-5, H-6' and H-6, H-1'); 7.97, 7.98, 8.00 (3 acetate signals); 8.1-9.1 (9 remaining cyclohexyl ring protons; doublet, CH_3, centered at 8.98, spacing 6 Hz).

iv. (1'R)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-β-D-glucopyranoside (50).

Compound 49 (3.57 g, 6.97 mmoles) was hydrogenated at 60 p.s.i. to yield a crystalline mass (2.48 g). Recrystallization from 95% ethanol afforded compound 50 (2.33 g, 87%), m.p. 126-127°, $[\alpha]_D^{24}$ - 50.4° (c, 1 in chloroform).

Anal. Calc'd. for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83.

Found: C, 58.86; H, 7.65.

P.m.r. data for 50, in chloroform-d: τ 4.78 (triplet, H-3, spacing of 9 Hz); 5.03 (triplet, H-2, spacing 8 Hz); 5.13 (triplet, H-4, spacing 9 Hz); 5.44 (doublet, H-1, spacing 8 Hz); 6.30-6.58 (multiplet, H-5, centered

6.44); 6.74-7.00 (multiplet, H-1', centered 6.87); 7.94, 7.96, 7.98 (3 acetate signals); 8.1-9.1 (9 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered at 8.73, spacing 6 Hz; doublet, CH_3, centered 9.01, spacing 6 Hz

v. Deacetylation.

Compound 50 (1 g, 2.85 mmoles) was deacetylated to yield crude 51 (0.64 g), $[\alpha]_D^{24}$ - 90.1° (c, 0.995 in water). Crystallization twice from an acetone-Skellysolve B mixture afforded compound 51 (0.6 g, 88%), m.p. 117-118°, $[\alpha]_D^{24}$ - 89.4° (c, 0.998 in 10% methanol-water).

Anal. Calc'd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29.

Found: C, 59.72; H, 9.27.

P.m.r. data for 51, in 15% methanol-d_4-deuterium oxide: τ 5.88 (doublet, H-1, spacing 8 Hz); 8.97 (doublet, 6-deoxy CH_3, spacing 6 Hz); 9.27 (doublet, CH_3, spacing 6 Hz).

22. (1'R)-*trans*-2'-Methylcyclohexyl 6-deoxy-α-D-glucopyranoside (53).

i. (1'R)-*trans*-2'-Methylcyclohexyl tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (52).

Compound 50 (1.85 g, 5.3 mmoles) was anomerized under reflux conditions for 1.5 h to yield an oil which crystallized upon the addition of Skellysolve B (1.6 g), $[\alpha]_D^{24}$ + 115.6° (c, 1.01 in chloroform). Recrystallization twice from Skellysolve B afforded compound 52 (1.2 g, 67%), m.p. 97-98°, $[\alpha]_D^{24}$ + 110.2° (c, 1 in chloroform).

Anal. Calc'd. for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83.

Found: C, 59.08; H, 7.57.

P.m.r. data for 52, in chloroform-d: τ 4.37-4.57 (quartet, H-3, centered at 4.47, spacing 9 Hz); 4.86 (doublet, H-1, spacing 4 Hz); 5.07-5.21 (quartet, H-2, centered at 5.14, spacing 4 Hz); 5.17 (triplet, H-4, spacing 9 Hz); 5.74-6.06 (multiplet, H-5, centered at 5.90); 6.88-7.20 (multiplet, H-1', centered at 7.04); 7.94, 7.98 (3 acetate groups in the ratio 2:1 respectively); 8.0-9.1 (9 remaining cyclohexyl ring protons; doublet, 6-deoxy CH_3, centered 8.85, spacing 6 Hz; doublet, CH_3, centered at 9.05, spacing 6 Hz).

ii. Deacetylation.

Compound 52 (0.5 g, 1.3 mmoles) was deacetylated to yield crude 53 (0.39 g), $[\alpha]_D^{24}$ + 85.2° (c, 1 in 10% methanol-water). Crystallization twice from an acetone-Skellysolve B mixture afforded compound 53 (0.3 g, 92%), m.p. 134-135°, $[\alpha]_D^{24}$ + 87.5° (c, 0.995 in 10% methanol-water).

Anal. Calc'd. for $C_{13}H_{24}O_5$: C, 59.98; H,9.29.

Found: C, 59.69; H, 9.06.

P.m.r. data for $\underset{\sim}{53}$, in 15% methanol-d_4-deuterium oxide: τ 4.98 (doublet, H-1, spacing 3.5 Hz); 6.40 (doublet, H-2, spacing 9 Hz by decoupling with H-1); 8.65 (doublet, 6-deoxy CH_3, spacing 6 Hz); 8.87 (doublet, CH_3, spacing 6 Hz).

TABLE 10

Carbon-13 chemical shifts in cyclohexyl D-glucopyranosides and (1'R)- and (1'S)-*trans*-2'-methylcyclohexyl D-glucopyranosides

	Chemical shifts (ppm) relative to TMS												
No.	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	CH_3
2	100.9	73.8	76.4	70.3	76.4	61.4	79.1 (79.9)	33.6* (33.9)	24.2 (23.9)	25.6 (26.9)	24.2 (23.9)	32.0* (31.9)	
5	104.0	74.1	76.6	70.1	76.2	61.3	87.2 (89.9)	38.5 (40.9)	34.0* (33.9)	25.2* (24.9)	25.0* (23.9)	33.8* (31.9)	18.3
6	100.2	73.5	76.5	70.1	76.2	61.2	84.0	37.5	33.8	25.2*	24.7*	31.3	18.6
4	96.9	71.9	73.8	70.3	72.3	61.2	77.1	31.6*	24.4*	25.6	24.2*	33.5*	
9	94.5	71.7	73.5	70.1	72.4	61.0	80.8	37.9	33.9	25.4*	24.7*	30.1	19.2
12	100.6	72.2	73.6	70.2	72.5	61.1	85.9	38.7	33.7	25.0	25.0	33.7	18.3

* Assignments of carbon-13 shifts in these positions is uncertain.

( ) Calculated carbon-13 shifts by a method in a book by Levy and Nelson (83) based on chemical shift parameters developed for substituted cyclohexanols. The calculated chemical shifts for compound 2 also apply to compound 4. Those calculated for compound 5 also apply to compounds 6, 9 and 12.

TABLE 11

Carbon-13 chemical shifts in (1'R)- and (1'S)-*trans*-2'-hydroxycyclohexyl D-glucopyranosides

	No.	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
		Chemical shifts (ppm) relative to TMS											
	13	103.6	74.2*	76.4	70.2	76.4	61.4	86.0	74.1*	32.8*	24.1*	23.8*	32.1*
β								(90.9)	(81.9)	(34.9)	(23.9)	(23.9)	(31.9)
	14	100.9	73.6*	76.4	70.3	76.4	61.4	83.8	73.3	32.6	24.0	23.8	30.2
α	17	95.2	71.8	73.5*	70.2	72.2	61.1	80.1	73.2*	33.0	24.0*	23.9*	28.9
	20	100.4	72.4	73.6	70.3	72.4	61.0	85.1	74.3	32.9*	23.9*	23.6*	32.1*

* Assignments of carbon-13 shifts in these positions are uncertain.

( ) Calculated carbon-13 shifts (83). Calculated shifts for compound 13 apply to all compounds shown in the table.

TABLE 12

Carbon-13 chemical shifts in (1'R)- and (1'S)-*trans*-2'-chlorocyclohexyl D-glucopyranosides

No.	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
							Chemical shifts (ppm) relative to TMS					
21	103.6	74.1	76.4	70.3	76.4	61.4	84.2	64.2	35.5	24.8*	23.6*	33.4
β							(91.9)	(64.9)	(35.9)	(23.9)	(23.9)	(30.9)
22	100.0	73.5	76.5	70.2	76.4	61.3	81.3	63.1	35.1	24.6*	23.1*	30.5
25 α	95.3	71.7	73.5	70.2	72.5	61.1	79.4	63.7	35.8	25.1*	23.4*	30.1
28	100.3	72.3	73.6	70.2	72.6	61.1	83.4	64.7	35.7	25.0*	23.8*	33.3

* Assignments of carbon-13 shifts in these positions are uncertain.

( ) Calculated carbon-13 chemical shifts (83). Calculated shifts for compound 21 apply to all compounds shown in the table.

TABLE 13

Carbon-13 chemical shifts in (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl D-glucopyranosides

	Chemical shifts (ppm) relative to TMS												
No.	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	CH_3
30	102.7	74.4	76.7	70.2	76.0	61.4	91.2	37.9*	34.8*	25.4	34.9*	39.9*	19.4 19.0
32	99.1	72.1	73.2	69.4	72.6	60.9	91.0	39.7*	35.1	25.4	35.1	37.7*	20.0 19.5

* Assignments of carbon-13 shifts in these positions is uncertain.

III. DISCUSSION

A. Carbon-13 chemical shift studies

The labelling system employed in the assignment of carbon-13 chemical shifts for the model compounds presented in Tables 10-13 is summarized in Fig. 6.

Assignments in the glucopyranose ring were made by a comparison with the published results for the chemical shifts of methyl α- and β-D-glucopyranosides (89). The chemical shifts occurring at C-2 and C-5 are reversed from their original assignments (89) due to recent results obtained in this laboratory on vicinal carbon-13 to proton coupling studies of simple glycopyranosides (75). No significant changes in the C-2 to C-6 resonances are observed, either among the model compounds studied or among those observed for methyl α- and β-D-glucopyranosides. However, large chemical shift changes are observed at C-1 and seem to be reflected in the pattern of equatorial substitution vicinal to the aglyconic carbon atom.

Assignments of the carbon-13 chemical shifts for the aglycon carbon atoms, especially at the 2' and 6' positions, must be approached with caution because it is expected that any rotational changes occurring about the glucosidic linkage could possibly be reflected in the chemical shift changes at these positions. These rotational changes, if occurring, would not affect the carbon-13 resonances at centers remote from the glucosidic bond system and their assignment is not critical to the subsequent discussion. Hence, the chemical shifts observed at the 3', 4' and 5' positions are assigned primarily on the basis of their expected calculated values. No significant changes are observed among the assigned values for C-3', -4' and -5' in the α- and β-linked glucopyranosides studied.

The chemical shifts at C-1' in all compounds and at C-2' in the mono-substituted (1'S) and (1'R) D-glucopyranosides can be assigned with confidence as these would be shifted significantly downfield relative to the observed chemical shifts for the unsubstituted carbon atoms; the C-1' chemical shift resonating at lowest field when compared with C-2'. The chemical shifts for the 2' and 6' positions of cyclohexyl β- and α-D-glucopyranosides 2 and 4 and their dimethyl derivatives 30 and 32 are also expected to occur downfield due to substitutional effects (α and/or β shift effect), but cannot be irrevocably assigned due to the ~ 2 ppm difference in observed chemical shifts occurring at these positions. Similarly, the assignments of carbon-13 shifts at the 6' position in the mono-substituted cyclohexyl D-glucopyranosides are not certain, although on the basis of the empirical rules for the calculation of chemical shifts (83) it is expected that these resonances would occur at slightly higher field than the chemical shifts observed at C-3'.

As was the case with the C-1 chemical shift of the glucoside moiety, significant differences are observed at C-1' of the aglycon and show similar trends to those observed at C-1. Namely, an equatorial substituent (CH_3, OH and Cl) on the side of the glucosidic linkage remote from the pyranoid ring oxygen atom (cf. compounds 5, 13 and 21, and 12,20 and 28) causes significant deshielding in the assigned values for the chemical shifts at C-1 and C-1' when compared to an equatorial substituent on the same side of the molecule as the ring oxygen atom (cf. compounds 6, 14 and 22 and 9, 17 and 25). Smaller chemical shift differences have been previously noted between the 2' and 6' positions of compounds 2 and 4 and between compounds 30 and 32. Differences are also noted between the chemical shifts at the 2' or 6' positions of cyclohexyl D-glucopyranosides 2 and 4 and the comparable methylene positions vicinal to the aglyconic carbon atom in the mono-substituted cyclohexyl D-glucopyranosides. These differences between the comparable methylene positions in the mono-substituted derivatives are real and cannot be explained by the γ effect associated with an equatorial substituent. According to Dalling and Grant (27), the substituent effect at the γ position is negligible when compared with the effects observed at the β and α positions.

In cyclohexanol, the 2' and 6' methylene carbons are in a similar conformational environment and no change in the carbon-13 shifts of these carbons is expected or observed (cf. Table 7). However, in the glucopyranosides under study, these methylene carbons are no longer equivalent due to the asymmetry of the glucosidic moiety and differences in carbon-13 shifts at the comparable 2' and/or 6' positions in the model compounds might be expected due to differences in the orientation of the aglycon with respect to the glucopyranoside ring. These differences have, in fact, been observed.

The chemical shift differences observed at the C-1, -1', -2' and/or -6' positions in the model compounds will be subsequently discussed in relation to an attempt to calculate the rotamer populations for the three staggered orientations of the cyclohexyl aglycon about the C-1' to O-1' bond. This consideration necessarily assumes that the cyclohexyl ring has the C1 conformation with the C-1' to O-1' bond and the equatorial substituent in a di-equatorial relationship. Evidence will now be presented from the observed chemical shifts of the methylcyclohexyl D-glucopyranosides, 5 and 6, 9 and 12, which will negate the possibility of conformational changes occurring in the cyclohexyl ring itself; that is, to the alternate chair or to one of several possible boat or skew forms.

The methyl substituted derivatives were chosen for this argument primarily because the chemical shift parameters for axial and equatorial substituents (either hydroxyl or methyl) in cyclohexanols have been well documentated in the literature. The compounds to be discussed are compared in Table 14.

Comparing cyclohexyl β-D-glucopyranoside (2) and (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (5), large changes are observed between the chemical shifts at C-1', C-2' and C-3'. These changes are normal for a diequatorial substituted cyclohexane ring and can be accounted for by applying the methyl substituent parameters observed by Dalling and Grant (27). An equatorial methyl substituent increases the chemical shifts at each of the vicinal β-carbons by a value of +8.9 ppm and increases the chemical shift of the α-carbon (point of methyl attachment) by +5.6 ppm. Smaller shift changes would occur at the γ and δ carbons but are insignificant. These parameters when added to the appropriate observed chemical shifts for compound 2 give excellent agreement with the observed chemical shifts for (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (5). A similar comparison can be drawn between the

TABLE 14

A comparison of observed chemical shifts for the cyclohexyl carbon atoms of cyclohexyl α- and β-D-glucopyranosides and their corresponding 2' methyl substituted derivatives

		Chemical shifts (ppm) relative to TMS						
	Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	CH_3
	2	79.1	33.6	24.2	25.6	24.2	32.0	
β	5	87.2	38.5	34.0	25.2	25.0	33.8	18.3
	6	84.0	37.5	33.8	25.2	24.7	31.3	18.6
	4	77.1	31.6	24.4	25.6	24.2	33.5	
α	9	80.8	37.9	33.9	25.4	24.7	30.1	19.2
	12	85.9	38.7	33.7	25.0	25.0	33.7	18.3

observed chemical shifts for cyclohexyl α-D-glucopyranoside (4) and (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (12). The shift changes occurring at the β and α carbons are normal and are accounted for in a similar manner to that described above. The chemical shift difference between the assigned values for C-1' in compound 2 and (1'R)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (6) is only 4.9 ppm and is similar to the β shift parameter observed in substituted cyclohexyl derivatives where the methyl substituent is in an axial orientation. If this is indeed the case for compound 6, then relative to the chemical shifts observed for compound 2, a similar change should be noted at C-3' and the chemical shifts at C-4' and C-6' should be strongly shielded by 5.2 ppm due to the γ effect associated with an axial methyl substituent. These large chemical shift changes are not observed. A similar argument can be applied to the observed chemical shift difference at C-1' for (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (9). Thus any conformational change occurring in the cyclohexyl ring which would place the methyl group in an axial environment can be discounted because the chemical shift changes due to this type of conformation are not observed.

Lastly, an examination of the chemical shifts for the methyl carbon atom supports the contention that in all cases the cyclohexyl ring has the C1 conformation with both the C-1' to O-1' bond and the methyl substituent in the di-equatorial form. The methyl carbon atom resonates between 18.3 and 19.2 ppm which is normal for the resonance observed in diequatorial *trans*-2-methylcyclohexanol (cf. Table 7). If the conformation of the cyclohexyl ring is such that C-1' to O-1' bond has obtained an axial orientation, it is expected that the methyl carbon chemical shift would be closer to the value of 16.2 ppm observed for *cis*-2-methylcyclohexanol (cf. Table 7), but this is not observed.

Boat or skew conformations in which the methyl group and the C-1' to O-1' bond maintain a di-equatorial relationship have not been negated entirely, but it is expected that such conformations would be of higher energy than the C1 conformation and changes in the carbon-13 spectra of carbon atoms remote form C-1', -2' (-6') would be expected. Such conformational changes in the cyclohexyl ring would occur at carbon centers remote from the glucosidic bond system and would be of little help in relieving possible steric or non-bonded interactions in the region of this bond.

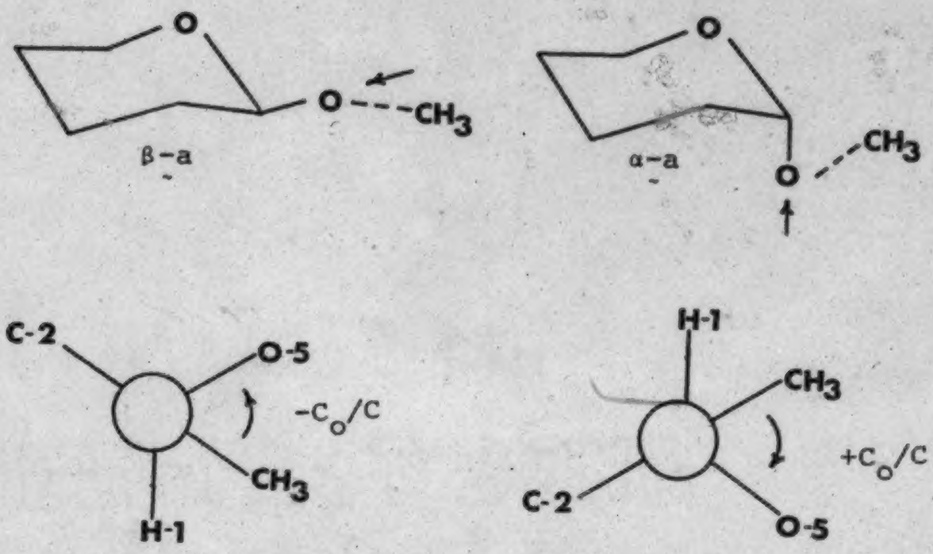
It is thus apparent that the large chemical shift differences observed at the C-1' position are not due to changes occurring in the expected C1 conformation of the aglycon with all substituents in an equatorial orientation. Furthermore, the magnitude and direction of these changes also occur at C-1 of the glucosidic moiety. Since the conformation of the glucosidic bond system might be presumed to be fixed by the *exo* anomeric effect, it is possible that the differences in carbon-13 chemical shifts occurring at C-1' and C-1 are the result of rotational changes about the C-1' to O-1' bond, hence changes in the orientation of the cyclohexyl aglycon with respect to the glucopyranoside ring. If any rotational changes are occurring that would necessarily alter the conformation about the glucosidic linkage, then these changes should also be reflected in the carbon-13 chemical shifts at the 2' and 6' positions; these, as mentioned earlier were observed.

B. Conformational properties of simple D-glucopyranosides in solution.

1. A consideration of methyl D-glucopyranosides.

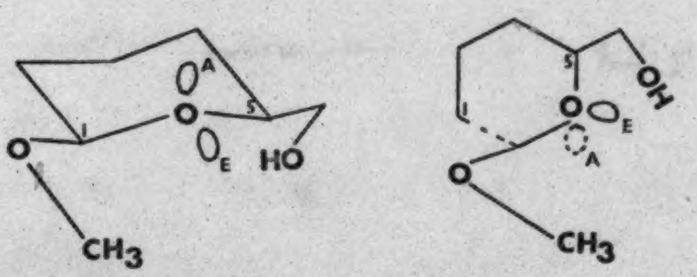
It was previously shown that, in solution, the methyl aglycon preferred the orientation as depicted in conformers α-a and β-a as shown in Figs. 9 and 10, respectively, both for reasons of the *exo* anomeric effect and a consideration of steric and non-bonded interactions. It was also noted (cf. Table 1) that the observed differences in molecular rotation between the methyl D-glucopyranosides and their corresponding D-glucopyranoses were constant at ±103° +4°. This contribution to rotation from the methoxy group at C-1 can be explained by referring to the formulas shown in Fig. 13. The Newman projection formulas as displayed in this figure are viewed in the direction shown. In both the α-a and β-a conformers, the aglyconic carbon atom is *gauche* to O-5 and *trans* or *anti*-periplanar to C-2; thus, the rotatory contribution from the C_O/C conformational unit is 0° or negligible and the observed rotational differences are easily explained by the contributory values of the C_O/O unit based on a torsion angle $\phi = \pm 60°$. This C_O/O asymmetric conformational unit has been assigned values ranging from ±105° (77) to ±115° (7,65).

For the α- and β-anomers, it is seen that the contribution to molecular rotation from the methoxy group is reasonably constant for both glucopyranosides. This observation would suggest that the methyl group is in a similar conformational environment for both anomers. Suitable conformational formulas showing the orientation of the methyl aglycon in enantiomeric like glucopyranosides are illustrated in Fig. 14. For the purposes of comparison, the conformational formulas for methyl β-D-glucopyranoside


O
O
CH3
β-a
O
CH3
α-a
C-2
O-5
-Co/C
CH3
H-1
H-1
CH3
+Co/C
C-2
O-5

$C_o/C - C_o/O = -100°$ $C_o/C + C_o/O = +107°$

Fig. 13: Conformational formulas in methyl α- and β-D-glucopyranosides showing the contribution to rotation from the methoxy group at C-1.


O
A
O
1
5
O
E
HO
CH3
OH
5
1
O
O
E
A
O
CH3

Me β-D-*gluco* Me α-L-*gluco*

Fig. 14: Conformational formulas showing the orientation of the methyl aglycon in enantiomeric like glucopyranosides.

and methyl α-L-glucopyranoside are shown. The following discussion will apply equally as well to the enantiomeric β- and α-D-glucopyranosides.

~~As seen~~, similar regions about the methyl aglycon exist for both anomers, except for the differences in orbital orientation at the ring oxygen atom. In the enantiomer with the β-D-*gluco* configuration, the methyl group sees both the axially and equatorially directed lobes of the ring oxygen atom. For the enantiomer with the α-L-*gluco* configuration, the axially orientated orbital is directed away from the methyl group which now views only the equatorial lobe of O-5. This difference in orbital orientation might be expected to be important from a rotational viewpoint, due to the way in which the plane of polarized light would view the enantiomeric like glucopyranoside molecules. However, due to the constant rotational differences observed for the D-glycopyranosides shown in Table 1, this orbital orientation apparently contributes little to molecular rotation.

2. Effects of substitution on the methyl carbon atom (aglyconic carbon) of methyl D-glucopyranosides.

The observed molecular rotations for ethyl, isopropyl and cyclohexyl D-glucopyranosides are shown in Table 15. It is interesting to note that the difference

TABLE 15

Molecular rotations for some α- and β-D-glucopyranosides

		α			β	
Aglycon	$[M]_D^{\circ}$	$\Delta[M]_D^{\circ *}$	$\Delta[M]_D^{Me\circ \dagger}$	$[M]_D^{\circ}$	$\Delta[M]_D^{\circ *}$	$\Delta[M]_D^{Me\circ \dagger}$
Methyl	+309	+107		-66	-100	
Ethyl	+316	+114	+ 7	-76	-110	-10
Isopropyl	+324	+122	+15	-91	-125	-25
Cyclohexyl	+349	+147	+40	-105	-139	-39

* Difference in molecular rotation from D-glucopyranose

† Difference in molecular rotation from methyl D-glucopyranoside.

in rotation from D-glucopyranose for each respective anomeric pair of glucosides shown is reasonably constant and tends to support the enantiomeric like relationship discussed previously for methyl D-glucopyranosides.

Substitution on the aglyconic carbon atom with carbon, as in the ethyl D-glucopyranosides, produces little change in molecular rotation when compared with the observed rotations for methyl D-glucopyranosides. The contribution to molecular rotation from the ethyl aglycon can similarily be explained by the C_o/O rotatory contribution based on the torsion angle ϕ ±60°. As the aglyconic carbon atom changes from one of primary to secondary substitution, as is the case with isopropyl and cyclohexyl D-glucopyranosides, the difference in molecular rotation from D-glucopyranose and methyl D-glucopyranoside is significantly larger and cannot easily be explained by the simple addition of the C_o/O rotatory contribution as was the case with simple methyl and ethyl D-glucopyranosides.

It has been shown that for these simple glycosides there exists considerable evidence for the *exo* anomeric effect and hence the preferred orientation of the aglyconic carbon atom *gauche* to the ring oxygen atom. Substitution on the aglyconic carbon atom, as in these more complex glucosides, is not expected to change the torsion angle ϕ much from ±60°, both from energy and steric considerations. However, for a secondary aglyconic carbon, the orientation of the aglycon itself about the C-1' to O-1' bond (the ψ torsion angle) is also expected to be influenced by the energies associated with non-bonded interactions and thereby influence the molecular rotation. An examination of the structural features about the glucosidic linkage in cyclohexyl D- glucopyranosides shows that in addition to the C_o/O four atom asymmetric conformational unit there exists two four atom units formed by the methylene carbon atoms vicinal to the aglyconic carbon atom and C-1 of the glucoside moiety. Depending on the orientation of the cyclohexyl aglycon, hence the torsion angle ψ, the contribution to molecular rotation from these C_o/C units will either be negligible, largely positive, or largely negative.

In order to assess the possible contributions to molecular rotation from the C_o/C units, it is necessary to examine the preferred orientations of the cyclohexyl aglycon about the glucosidic linkage. For the purposes of simplification, this examination will consist of an analysis of the non-bonded interaction energies associated with the three staggered conformers for the orientation of the cyclohexyl ring, where ψ = +60°, -60° and 180°. In this consideration, and all subsequent considerations involving the cyclohexyl ring conformers, the torsion angle ϕ is presumably fixed close to 60° by the nature of the *exo* anomeric effect. The three staggered conformers for cyclohexyl β-D-glucopyranoside are shown in Fig. 15. The Newman projection formulas, viewed down the O-1' to C-1' bond are also shown in this figure to illustrate the sign of the contribution to molecular rotation made by the C_O/C asymmetric conformational units.

The calculation of the non-bonded interaction energies associated with the three staggered conformers for cyclohexyl β-D-glucopyranoside are shown in Table 16. The energies associated with the *gauche* interactions are not shown in this table as these interactions are common to all conformers. The energies quoted for the *syn*-diaxial-like interactions are taken from a book by Stoddart (56) and references quoted therein.

From a consideration of only the energies associated with the *syn*-diaxial-like interactions, the calculations show that the favoured conformers for cyclohexyl β-D-glucopyranoside are in the order $\underset{\sim}{d} > \underset{\sim}{e} > \underset{\sim}{f}$. However, it must be pointed out that the differences in energy between these conformers is not very large and it is expected that the differences in free energy associated with the conversion of one conformer to another are not that great. Therefore, as a first approximation,

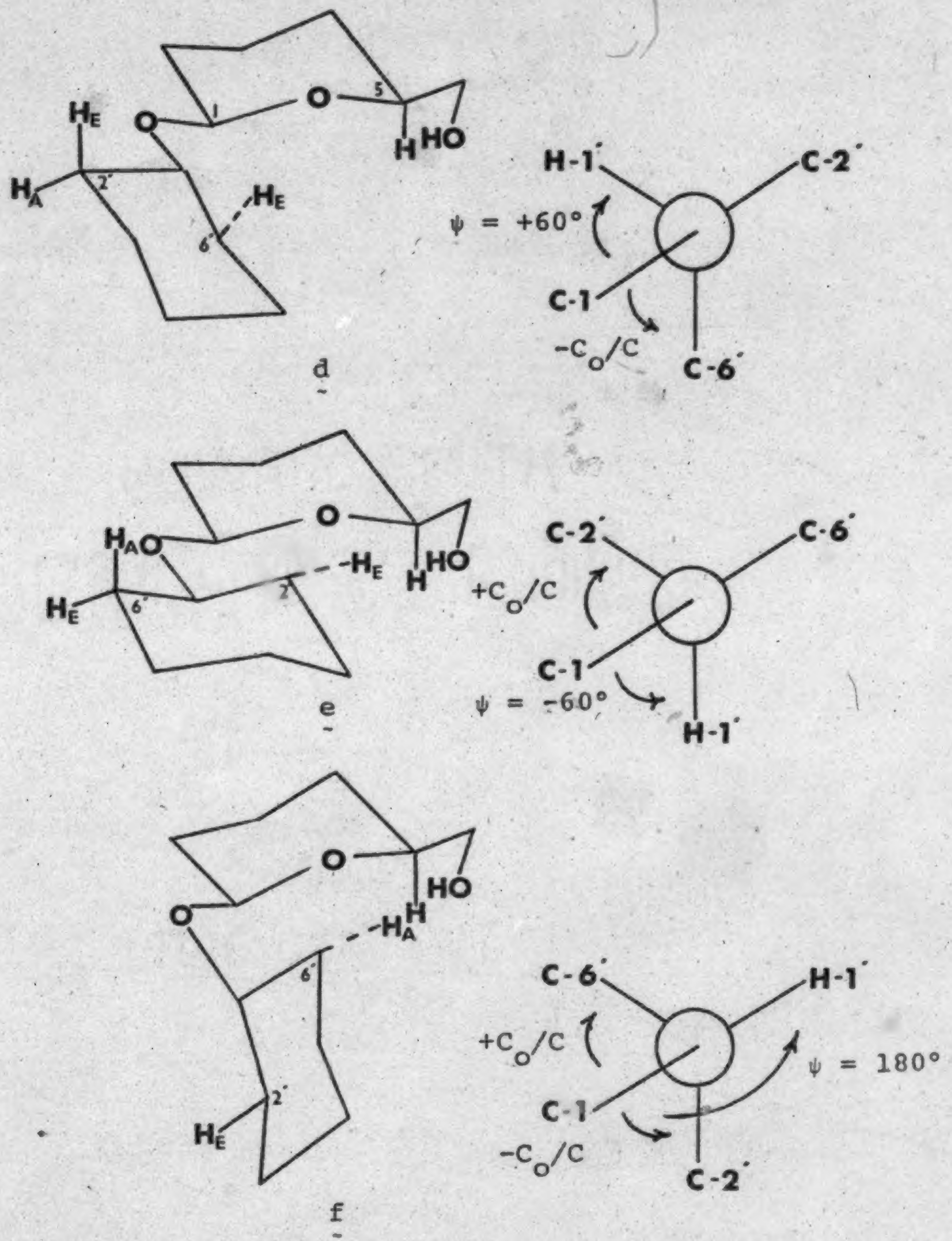

H_E
O
1
O
5
H
HO
H_A
2'
H_E
6'
H-1'
C-2'
ψ = +60°
C-1
-C_O/C
C-6'
d
H_AO
O
H
HO
-H_E
2'
H_E
6'
C-2'
C-6'
+C_O/C
C-1
ψ = -60°
H-1'
e
O
HO
O
-H_A
H
6'
2'
H_E
C-6'
H-1'
+C_O/C
ψ = 180°
C-1
-C_O/C
C-2'
f

Fig. 15: The three staggered d, e and f conformers for cyclohexyl β-D-glucopyranoside. Newman projection formulas showing the sign of the C_O/C parameter.

TABLE 16

A non-bonded interaction analysis for the three staggered d, e and f conformers of cyclohexyl β-D-glucopyranoside

	Non-bonded interactions		
Conformer	*Gauche*	*Syn*-diaxial	Energy (Kcal/mole)
d	C/H	O//H	0.45
	C/C	C//H	0.9
	H/e		1.35
	3C/e		
e	C/H	C//O	2.5
	C/C	H//H	
	H/e		2.5
	3C/e		
f	C/H	C//O	2.5
	C/C	C//H	0.9
	H/e		3.4
	3C/e		

it is seen that in the more favoured conformer d the contribution to molecular rotation from the C_o/C parameter is negative (cf. Fig. 15). As observed in Table 15, the difference in molecular rotation between cyclohexyl β-D-glucopyranoside and methyl β-D-glucopyranoside is -39°. In both of these glucosides it is assumed that the torsion angle ϕ is constant at +60° and therefore the contribution to molecular rotation from the C_o/O parameter is the same for both compounds.

The residual molecular rotation observed for cyclohexyl β-D-glucopyranoside, therefore, must come from the C_o/C asymmetric conformational units which are not found in methyl β-D-glucopyranoside. Depending on the value chosen for this C_o/C parameter and the relative populations of the other two conformers in solution, the preference for conformer d on the basis of non-bonded interaction energies could explain the residual -39° rotation observed. An experimental basis for the assignment of a value to this C_o/C conformational unit is to be presented shortly as well as a method to calculate the relative populations of d, e and f conformers in solution.

The three staggered conformers for cyclohexyl α-D-glucopyranoside as well as the appropriate Newman projection formulas are shown in Fig. 16. The non-bonded energies associated with the *syn*-diaxial-like interactions in conformers d, e and f are shown in Table 17. The

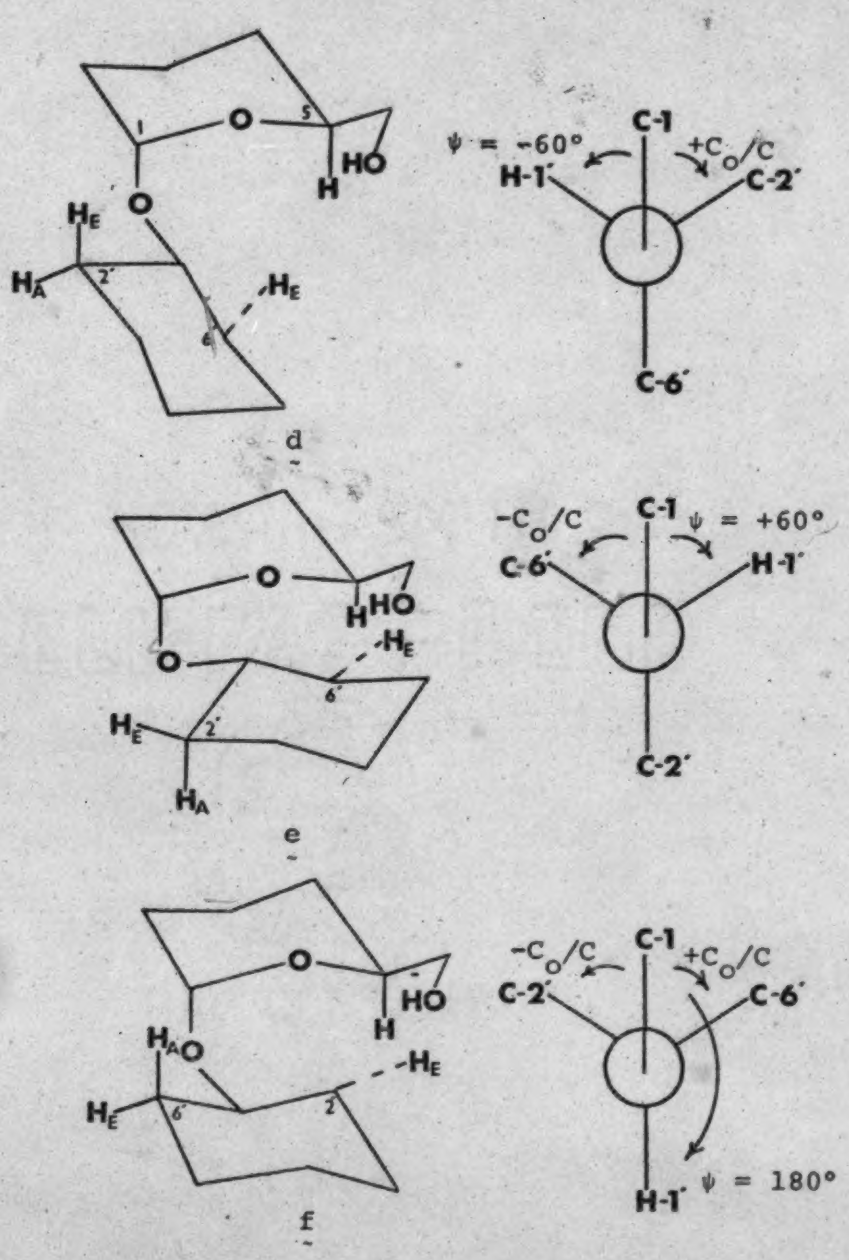

1
O
5
HO
H
O
H_E
H_A
2'
H_E
6'
ψ = -60°
C-1
+C_O/C
H-1'
C-2'
C-6'
d
O
H
HO
H_E
O
6'
H_E
2'
H_A
-C_O/C
C-1
ψ = +60°
C-6'
H-1'
C-2'
e
O
HO
H
H_A
O
H_E
H_E
6'
2'
-C_O/C
C-1
+C_O/C
C-2'
C-6'
ψ = 180°
H-1'
f

Fig. 16. The three staggered d, e and f conformers for cyclohexyl α-D-glucopyranoside. Newman projection formulas showing the sign of the C_O/C parameter.

TABLE 17

Non-bonded *syn*-diaxial like interactions for the three staggered *d*, *e* and *f* conformers for cyclohexyl α-D-glucopyranoside

Conformer	*Syn*-diaxial interaction	Energy (Kcal/mole)
d	O//H	0.45
	C//H	0.9
		1.35
e	C//O	2.5
	H//H	
		2.5
f	C//O	2.5
	C//H	0.9
		3.4

calculations show that conformer *d* is the more favoured form in solution. In this conformer, the sign of the C_o/C parameter is positive. In a like manner to that described above, a substantial population of conformer *d* in solution could explain the residual molecular rotation of +40° observed between cyclohexyl α-D-glucopyranoside and methyl α-D-glucopyranoside (cf. Table 15).

C. Conformational properties of cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides in solution.

1. An experimental basis for the assignment of a value to the C_o/C parameter.

In order to properly assign a value to the rotatory contribution from the C_o/C parameters in the three staggered *d*, *e* and *f* conformers, it is essential to search for a compound in which one of these conformers would exist almost exclusively in solution. An examination of the optical data presented in Table 18 reveals that (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (*9*) exhibits the largest change in molecular rotation when compared with its corresponding methyl D-glucopyranoside. In compound *9*, the methyl group at C-2' forms a dextrorotatory screw pattern with the aglyconic oxygen atom O-1'. As was

TABLE 18

Observed molecular rotations of cyclohexyl, (1'R)- and (1'S)-*trans*-2'-methylcyclohexyl D-glucopyranosides

Compound No.		$[M]_D$	$\Delta[M]_D$*
2		-104.7	- 38.7
5	(β-S)†	+ 28.2	+ 94.2
6	(β-R)†	-199.5	-133.5
4		+349.4	+ 40.4
9	(α-S)†	+476.4	+167.4
12	(α-R)†	+260.3	- 48.7

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* Difference in molecular rotation from methyl D-glucopyranoside.

† This notation will be used in the remaining discussion to denote the configuration of the substituted *trans*-2'-cyclohexyl D-glucopyranosides. For example, (α-R) denotes, in this particular table, (1'R)*trans*-2'-methylcyclohexyl α-D-glucopyranoside.

previously mentioned (cf. Table 5), this C/O parameter was assigned a value of +50°. Subtraction of this contribution to molecular rotation from the rotation observed for compound 9, still leaves a residual difference of +117.4° when compared with the rotation of methyl α-D-glucopyranoside. The possible conformational equilibria for compound 9 are presented in Fig. 17.

Calculation of the non-bonded interaction energies for the unsubstituted cyclohexyl ring has shown that the preferred conformers are in the order d > e > f. Referring to Fig. 17, it is seen that in conformer d the methyl substituent is well away from possible steric interactions with the glucopyranose ring, especially from interactions involving the hydroxymethyl function and the axial hydrogen at C-5. Conformer e places the methyl group into close proximity with the ring oxygen atom and introduces steric crowding with the hydroxymethyl function. The methyl substituent in conformer f is situated well away from the glucopyranose ring; however, there is a slight steric interaction between the axial hydrogen at C-6', the ring oxygen atom and the hydroxymethyl function. Thus it is seen, that conformer d can be predicted to exist almost exclusively in solution, both from a consideration of the non-bonded interaction energies associated with *syn*-diaxial-like interactions involving the cyclohexyl ring and from steric interactions involving the methyl substituent.

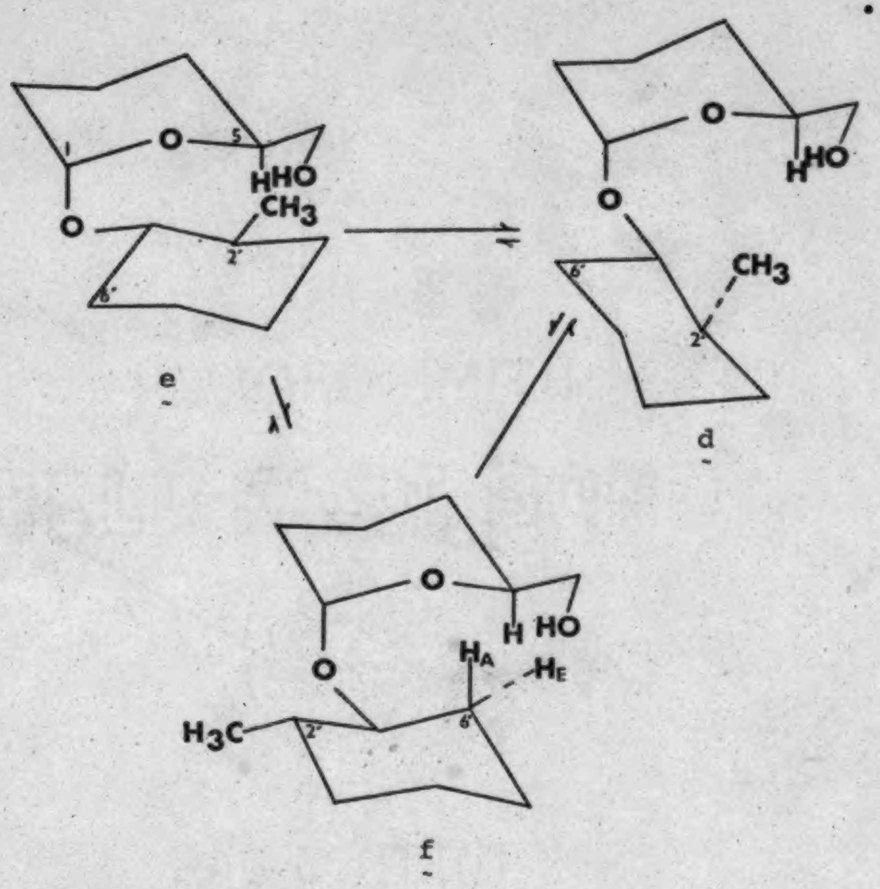

1
O
5
H
HO
O
CH3
2'
6'
e
d
f
O
H
HO
O
6'
CH3
2'
O
H HO
O
HA
HE
H3C
2'
6'

Fig. 17: Conformational equilibria involving the three staggered d, e and f conformers for (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (9)

The relative importance of conformers e and f are more difficult to predict. Conformer e is slightly more favoured than conformer f from a consideration of the energies associated with *syn*-diaxial-like interactions but is less favoured from a consideration of steric interactions involving the glucopyranose ring.

The evaluation of the optical rotation data accumulated in the experimental portion of this thesis and related to substitutional effects on rotation arising from the introduction of substituents (CH_3,OH or Cl) at the C-2' position of cyclohexyl α- and β-D-glucopyranosides depends on the value given to this C_o/C parameter and hence the populations assigned to the d, e and f conformers of compound 9. These populations, at present, cannot be assigned with accuracy. Rather than to assign a zero population to certain conformers, it was decided to give obviously unfavourable structures populations of 0.05 ± 0.05 mole fractions. Thus, the free energy found for these unfavourable conformers can be expected to be in the range of 1.3 to infinite Kcal/mole greater than that found for conformers which should be more favourable in solution from a consideration of the energies associated with both steric and *syn*-diaxial-like interactions. Such an energy range appears in line with the energy differences for cyclohexyl α- and β-D-glucopyranosides inferred in Tables 16 and 17. The relative populations for the three staggered orientations of the methylcyclohexyl aglycon in compound 9 are therefore arbitrarily assinged as follows.

Conformer	Population
d	0.85 ± 0.05
e	0.05 ± 0.05
f	0.10 ± 0.05

No other justification other than what has been mentioned, can be given for the arbitrarily chosen mole fractions for the conformers of compound 9 and it is important that the reader bears this matter in mind. The observed optical rotation data for the model compounds chosen for this study, therefore, cannot be evaluated with accuracy. At best, the detection of trends, based on reasonable assumptions is anticipated.

Since in conformer f, the sum of the C_o/C rotatory contributions must equal zero, the residual rotation of +117° observed for compound 9 must be considered derived from the sum of the $+C_o/C$ parameter in conformer d and the $-C_o/C$ parameter in conformer e. The maximum value for the C_o/C parameter is thus calculated from the following expression:

$$X\ (n_d - n_e) = 117°$$

where

$X \equiv$ maximum value for the C_o/C parameter (°)

$n_d \equiv$ rotamer population for conformer d which has been given the value $n = 0.85$.

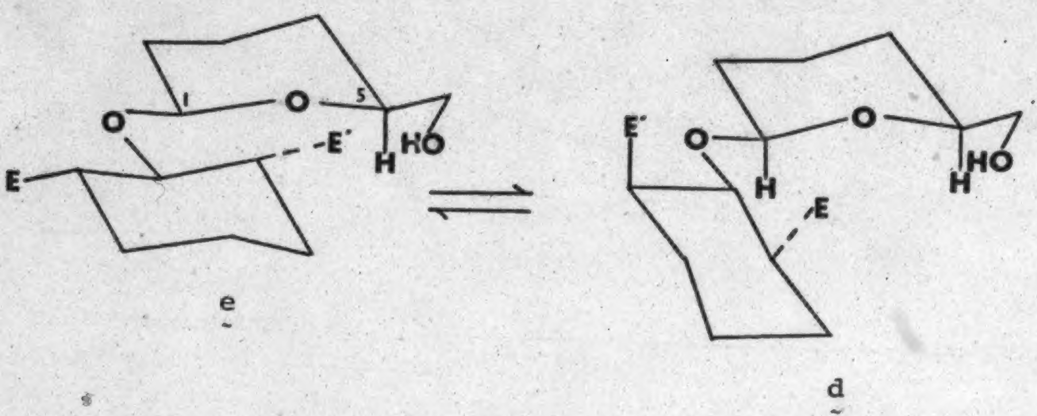
$n_e \equiv$ rotamer population for conformer e which has been given the value $n = 0.05$.

This expression gives a value of +146° for the C_O/C parameter, which is to be used in all subsequent calculations of the populations for conformers d, e and f.

2. Calculation of the d, e and f rotamer populations for cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides.

Owing to the difficulty in assessing the population of conformer f in solution due to the zero rotational contribution from the sum of the C_O/C asymmetric conformational units, the amount of this conformer in solution will arbitrarily be set at 10 ± 5%. This conformer should be less likely to occur in solution from a consideration of the energies associated with *syn*-diaxial-like non-bonded interactions, but might be more important in some compounds due to the steric effects associated with substituents on the carbon atoms vicinal to the aglyconic carbon atom. With this assumption, the relative populations of conformers d and e need now only to be considered. The conformational equilibria involving these two conformers in β- and α-D-glucopyranosides is shown in Fig. 18.

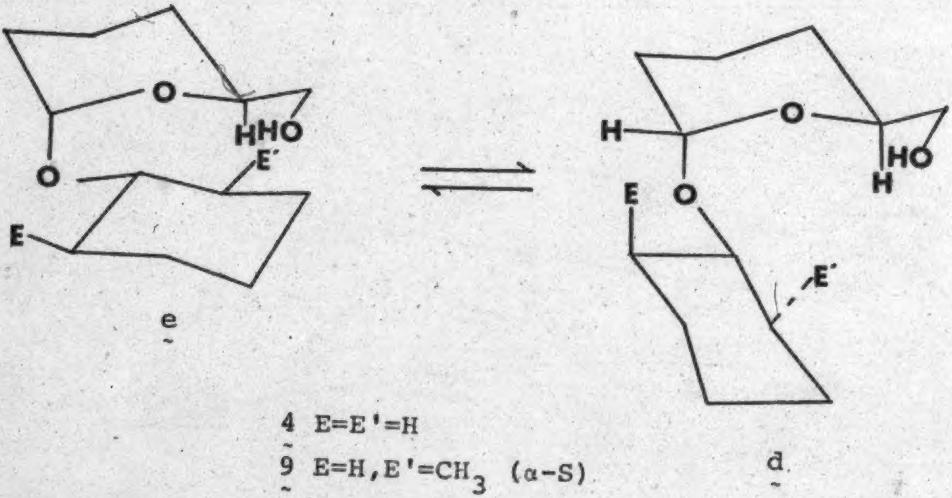
This calculation of rotamer populations is based on the observed molecular rotations of methyl α- and β-D-glucopyranosides and the rotations of the compounds chosen for this study. It was seen that the differences


1
5
O
O
E'
HO
H
E
e
E'
O
O
H
HO
H
E
d

2 E=E'=H

5 E=CH_3,E'=H (β-S)

6 E=H,E'=CH_3 (β-S)


O
HHO
E'
O
E
e
H
O
HO
H
E
O
E'
d

4 E=E'=H

9 E=H,E'=CH_3 (α-S)

12 E=CH_3,E'=H (α-R)

Fig. 18: Conformational equilibria between conformers e and d for β- and α-D-glucopyranosides.

in observed molecular rotation from D-glucopyranose for these simple methyl glucosides could be explained by the value of the C_o/O parameter based on a torsion angle $\phi = \pm 60°$. It is assumed that the value for the torsion angle ϕ, hence the value of the C_o/O parameter is common to all the compounds to be discussed. The calculations of the relative populations for conformers $\underset{\sim}{d}$ and $\underset{\sim}{e}$ are then based solely on the contribution to rotation from the C_o/C conformational units, the sum of which is expected to be either negative or positive depending on the conformer most preferred in solution. The following equations are to be used to calculate the relative population in solution for cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides.

β-D-glucosides

$$[M_{obs}]_D^{\beta} = [M]_D^{\beta Me} \pm C/O + 146\ (n_{\underset{\sim}{e}} - n_{\underset{\sim}{d}})$$

α-D-glucosides

$$[M_{obs}]_D^{\alpha} = [M]_D^{\alpha Me} \pm C/O + 146\ (n_{\underset{\sim}{d}} - n_{\underset{\sim}{e}})$$

where

$[M_{obs}]_D$ ≡ observed molecular rotation for the α- or β-D-glucopyranoside in (°)

$[M]_D^{\beta Me}$ ≡ observed molecular rotation for methyl β-D-glucopyranoside. $[M]_D^{\beta} = -66°$

$[M]_D^{\alpha Me}$ ≡ observed molecular rotation for methyl α-D-glucopyranoside, $[M]_D^{\alpha Me} = 309°$

C/O ≡ applies only to the methylcyclohexyl D-glucopyranosides. The value of C/O = ± 50° depending on whether the glucoside has the (1'R) or (1'S) configuration

n ≡ the relative populations of conformers $\underset{\sim}{e}$ or $\underset{\sim}{d}$. $n_{\underset{\sim}{e}} + n_{\underset{\sim}{d}} = 0.9$.

Sample calculations are given below for (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside ($\underset{\sim}{5}$) and (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside ($\underset{\sim}{12}$). The calculated values for the populations of conformers $\underset{\sim}{d}$ and $\underset{\sim}{e}$ are rounded to the nearest 5%. All subsequent calculated values are similarly reported.

Compound 5

$$[M_{obs}]_D^{\beta} = [M]_D^{\beta Me} + C/O + 146\,(n_{\underset{\sim}{e}} - n_{\underset{\sim}{d}})$$

$$+28.2 = -66 + 50 + 146\,(n_{\underset{\sim}{e}} - n_{\underset{\sim}{d}})$$

$$\begin{aligned} n_{\underset{\sim}{e}} - n_{\underset{\sim}{d}} &= 0.30 \\ n_{\underset{\sim}{e}} + n_{\underset{\sim}{d}} &= \underline{0.90} \\ 2n_{\underset{\sim}{e}} &= 1.20 \\ n_{\underset{\sim}{e}} &= 0.60 \end{aligned}$$

$n_{\underset{\sim}{e}} = 0.60$ $\quad$ $n_{\underset{\sim}{d}} = 0.30$ $\quad$ $n_{\underset{\sim}{f}} = 0.10$.

Compound 12

$$[M_{obs}]_D^{\alpha} = [M]_D^{\alpha Me} - C/O + 146\,(n_d - n_e)$$

$$260 = 309 - 50 + 146\,(n_d - n_e)$$

$$n_d - n_e = 0$$

$$n_d + n_e = 0.9$$

$n_d = 0.45$ $n_e = 0.45$ $n_f = 0.10$

The calculated values for the relative populations of conformers d and e for cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides are summarized in Table 19. The most favoured rotamer in solution for cyclohexyl β- and α-D-glucopyranosides (2 and 4) was calculated to be d. Since in both compounds the equatorial substituents at E' and E are hydrogens, the equilibrium between conformers e and d should be directed mainly by the energies associated with *syn*-diaxial like non-bonded interactions in these two conformers. This was shown previously to favour conformer d. The equatorial hydrogen at E' in conformer e is directed towards the substituents at C-5 and hence it is expected that the equilibrium would shift more in favour of conformer d.

When the equatorial substituent at E' is methyl, as in compounds 6 and 9, the equilibrium should be shifted

TABLE 19

Relative populations for the d, e, and f conformers in cyclohexyl, (1'R)- and (1'S)-*trans*-2'-methylcyclohexyl D-glucopyranosides

Compound No.	d	e	f
2	0.60	0.30	0.10
5 (β-S)	0.30	0.60	0.10
6 (β-R)	0.75	0.15	0.10
4	0.60	0.30	0.10
9 (α-S)	0.85	0.05	0.10
12 (α-R)	0.45	0.45	0.10

more in favour of the d conformer, as now there are severe interactions between the methyl substituent, the ring oxygen atom and the hydroxymethyl function at C-5. The calculations based on the observed molecular rotations for these two compounds illustrate this shift in conformational equilibrium.

A consideration of the effects of methyl substitution at E shows that for (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (5) the equilibrium is now directed more in favour of conformer e, despite the lower energy found for conformer d on the basis of *syn*-diaxial-like interactions However, in conformer d the methyl substituent is directed underneath the glucopyranose ring and severe steric interactions exist between the axial hydrogens at C-1 and C-5. Conformer d, therefore, must be less favoured from this consideration.

Substitution at E, as in (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (12) seems to shift the equilibrium neither in favour of conformers d nor e Conformer e directs the methyl substituents well away from the glucopyranose ring and no severe steric interactions exist; except the *syn*-diaxial-like interaction between the C-6' methylene group and the ring oxygen atom. Some steric interaction exists between the methyl substituent and the equatorial hydrogen at C-1 in conformer d, but this conformer as shown, has a lower energy than conformer e on the basis of *syn*-diaxial-like interactions. The calculations, therefore, seem to show a compromise between the energies associated with *syn*-diaxial-like interactions and the energies due to steric effects involving substituent groups.

The calculation of rotamer populations by the use of molecular rotation data, therefore, seems to correlate well with considerations based on *syn*-diaxial-like non-bonded interactions and steric interactions associated with equatorial substituents. The method has at least shown the trend in conformational equilibrium. Whether the calculated numerical values are meaningful is questionable, as it was assumed in all cases that the torsion angle ϕ was constant at 60° and the maximum value allowed for the C_o/C parameter was fixed by assuming values for the rotamer populations of compound 9.

3. Correlation of carbon-13 chemical shifts with the calculated populations for conformers d, e and f.

Differences in the assigned carbon-13 chemical shifts occurring at C-1, -1', -6', and/or -2' in cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides were previously noted. The fact that differences in the c.m.r. spectra of these compounds occur, would seem to indicate the presence of the type of conformational equilibria discussed. An attempt, therefore, will be made to correlate this carbon-13 data with the rotamer populations just calculated. The assigned values of the carbon-13 chemical shifts to be discussed are presented in Table 20. The calculated values for the chemical shifts at the 2' and/or 6' methylene carbon atoms by a method about to be illustrated are also shown in this table.

In order to facilitate the calculation of carbon-13 chemical shifts, it is necessary to examine the relative conformational positions in conformers d, e and f, that each methylene carbon in cyclohexyl D-glucopyranosides (C-2' and C-6') and in *trans*-2'-methylcyclohexyl D-glucopyranosides (C-6') occupies. For reference these positions will be characterized by the *syn*-diaxial-like interactions associated with the methylene carbon atoms. These relative positions are summarized in Table 21. There remains now to assign a value to the carbon-13 shifts of the methylene carbons at the conformational positions characterized.

From an analysis of the three staggered conformers for (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (9), it was shown that conformer d existed almost exclusively in solution. The observed carbon-13 chemical shift at the C-6' methylene carbon atom is 30.1 ppm. Therefore, the value assigned to the methylene carbon atom characterized by C//H must be small. A value of 30 ppm will be thus assigned to the methylene carbon in this position. In (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (12), the calculations

TABLE 20

Variation in the carbon-13 chemical shifts at C-1, -1', -2' and/or -6' in cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides

	C.m.r. parameters (ppm) from TMS					Calculated chemical shifts (ppm)	
Compound No.	C-1	C-1'	C-2'	C-6'	CH_3	C-2'	C-6'
2	100.9	79.1	33.6	32.0	—	33.2	31.4
5 (β-S)	104.0	87.2	—	33.8	18.3	—	33.9
6 (β-R)	100.2	84.0	—	31.3	18.6	—	31.0
4	96.9	77.1	31.6	33.5	—	31.4	33.2
9 (α-S)	94.5	80.8	—	30.1	19.2	—	30.5
12 (α-R)	100.6	85.9	—	33.7	18.3	—	33.6

TABLE 21

The relative orientation of the methylene carbon in cyclohexyl, (1'R)- and (1'S)-*trans*-2'-methylcyclohexyl D-glucopyranosides

Methylene position	Compound	d	e	f
C-2'	2 (β-cyclohexyl)			
C-6'	4 (α-cyclohexyl)	C//e (33 ppm)*	C//O (35 ppm)*	C//H (30 ppm)*
C-6'	5 (β-S)			
C-6'	12 (α-R)			
C-2'	4 (α-cyclohexyl			
C-6'	2 (β-cyclohexyl)	C//H (30 ppm)*	C//e (33 ppm)*	C//O (35 ppm)*
C-6'	6 (β-R)			
C-6'	9 (α-S)			

( )* Indicates the assigned value to the carbon-13 chemical shift of the methylene carbon atom in the particular conformer characterized by the *syn*-diaxial-like interaction.

showed that the populations of conformers d and e were equal and the observed chemical shift for the methylene carbon atom at C-6' is 33.7 ppm. Therefore, the values assigned to the chemical shifts characterized by C//e and C//O must both be relatively larger than the value of 30 ppm assigned to the C//H position. On going from compound 12 to (1'S)-*trans*-2'- methylcyclohexyl β-D-glucopyranoside (5), the population of conformer e is increased to 60%, the population of d is decreased to 30% and the population of conformer f remains the same at 10%. The chemical shift at the C-6' methylene carbon in both compounds 5 and 12 remains unchanged. Therefore, the value of the chemical shift occuring at the position characterized by C//O must be larger than the value given to the C//e position. These chemical shifts are arbitrarily assigned at 35 ppm for C//O and 33 ppm for C//e. The values assigned to the carbon-13 chemical shifts thus characterized are summarized in Table 21.

Values for the C-2' and/or C-6' methylene carbon atoms in cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides may then be calculated by using the numerical values of the calculated rotamer populations for each compound and the values assigned to the carbon-13 resonances occurring in each of conformers d, e and f. An example of this calculation is given below for (1'R)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (6), where the relative populations in conformers d, e and f, respectively, were estimated to be 75%, 15%, and 10%.

Calculation of the ^{13}C shift at C-6' in compound 6

$$\delta_{calc} = n\ (C//H) + n\ (C//e) + n\ (C//O)$$

$$= 0.75\ (30) + 0.15\ (33) + 0.10\ (35)$$

$$\delta_{calc} = 31.0 \text{ ppm.}$$

The calculated carbon-13 shifts and the assigned chemical shifts as shown in Table 20 are in good agreement, which lends some credibility to the values arbitrarily given to the resonances characterized by C//H, C//e and C//O and lends partial support to the treatment of the observed optical rotation data.

The observed chemical shift changes occurring at C-1 and C-1' are more difficult to rationalize. Consider, first of all, the β-D-glucopyranosides. In (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (5) the chemical shift at C-1 of 104.0 ppm compares favourably with that observed for methyl β-D-glucopyranoside (89) and methyl β-D-cellobioside (95). Calculation of rotamer populations showed that compound 5 existed predominantly as conformer e in solution. In contrast, the C-1 chemical shifts for compounds 2 and 6 are shielded by ~ 3.5 ppm when compared with the shift observed for compound **5**. Cyclohexyl and (1'R)-*trans*-2'-methylcyclohexyl β-D-glucopyranosides (**2** and **6**) were shown to exist largely in conformer **d** in solution. In this particular conformer, for both compounds, the hydrogens at the C-6' methylene carbon are directed toward the glucopyranose ring and interact with the axial hydrogen at C-1. Such an interaction involving C-1 is not found in compound **5**. Furthermore, the values of the carbon-13 shifts at C-6' for compounds **2** and **6** are shielded relative to that observed at C-6' for compound **5**. It is thus apparent that steric or non-bonded interactions in conformer **d** are responsible for the observed chemical shift changes occurring at C-1. Presumably, the same factors are responsible for the observed shielding in the C-1' resonance of compound **6** compared with that observed in compound **5**. The resonance of the methyl carbon atom remains unchanged for compounds **5** and **6**, where its orientation in the **e** and **d** conformers, respectively, is well away from steric or non-bonded interactions with the glucopyranose ring.

The C-1 chemical shift for (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (**12**) compares favourably with that observed for methyl α-D-glucopyranoside (89) and methyl β-D-maltopyranoside (95). The chemical shift at this position in compounds **4** and **9** is shielded and, in a like manner to that described above, this shielding seems to be controlled by the relative proportions of conformer **d** in solution. A slight shielding of ~ 1 ppm is observed in the chemical shift of the methyl carbon in (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (**12**) as compared with that observed in the corresponding (1'S)-derivative (**9**). This can possibly be explained by the steric interaction between the methyl substituent and the hydrogen at C-1, which is present in conformer **d** of compound **12**.

4. X-ray crystal structure ~~of~~ (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (**5**).

The preceding discussion on the calculation of rotamer populations for the *trans*-2'-methylcyclohexyl D-glucopyranosides has shown that the relative proportions of conformers **d**, **e** and **f** in solution were controlled mainly by steric interactions involving the methyl substituent. The crystal structure analyses of these substituted cyclohexyl D-glucopyranosides were, therefore, undertaken (31) to obtain possible supporting evidence in favour of the calculation of rotamer populations based on optical rotation data. At the time of this writing, only the crystal structure of compound **5** is available.

The values for the torsion angles (ϕ, ψ) from the crystal structure of compound **5** are (+31.7°, -32.6°). Similar values for the torsion angles (ϕ, ψ) are found for methyl β-D-cellobioside (71). Differences in the torsion angle ϕ in the solid state from that predicted in solution (ϕ = ±60°) have been previously noted for 1,4-β- and 1,4-α-linked disaccharides (cf. Table 3). These differences were attributed to the intermolecular and crystal packing forces present in the solid state which were expected to play an important part in establishing the conformation of these compounds.

On the basis of optical rotation data, (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside was shown to exist predominantly in conformer **e** in which the torsion angles (ϕ, ψ) are (+60°, -60°). These values for the torsion angles (ϕ, ψ) in solution are not far different from those observed in the solid state. If, indeed, the value for the torsion angle ϕ in solution is governed by the *exo* anomeric effect, as was assumed, then the conformation for compound **5** found in the solid state correlates nicely with that predicted to exist most favourably in solution.

D. Conformational properties of *trans*-2'-hydroxycyclohexyl and *trans*-2'-chlorocyclohexyl D-glucopyranosides in solution.

A study of the conformational equilibria involving the three staggered orientations of the aglycon (ψ = -60°,

+60°, 180°) in the hydroxycyclohexyl and chlorocyclohexyl D-glucopyranosides was undertaken primarily to assess the effect that polar substituents had on the conformation about the glucosidic bond system. Apart from the steric effects associated with these substituent groups, the polar nature of the hydroxy or chloro substituent might be expected to influence the relative populations found in solution for conformers d, e and f. Hydrogen bonding with the solvent or the glucopyranose ring in the hydroxycyclohexyl derivatives might also be expected to be important in favouring one conformer over another.

The observed molecular rotations for these D-glucosides are presented in Table 22. Quite apparent from this table is the striking similarity between the observed molecular rotations for the 2'-chloro and 2'-hydroxy substituted D-glucosides and the rotations for the 2'-methyl derivatives presented in Table 18. The only large change in molecular rotation occurs in (1'R)-*trans*-2'-hydroxycyclohexyl β-D-glucopyranoside (14).

The relative populations in conformers d, e and f for the compounds shown in Table 22, are calculated in a similar manner to those of the *trans*-2'-methylcyclohexyl D-glucopyranosides. All assumptions are the same. The C/O parameter for the methyl group and the aglyconic oxygen atom in a *gauche* relationship is necessarily replaced by the O/O parameter for the hydroxy derivatives and the Cl/O

TABLE 22

Observed molecular rotations for *trans*-2'-hydroxycyclohexyl and *trans*-2'-chlorocyclohexyl D-glucopyranosides

Compound	Substituent at 2'	$[M]_D^{\circ}$
13 (β-S)	OH	+ 25.9
21	Cl	+ 28.5
14 (β-R)	OH	-170.3
22	Cl	-199.1
17 (α-S)	OH	+477.0
25	Cl	+477.5
20 (α-R)	OH	+259.1
28	Cl	+252.8

TABLE 23

Relative populations for the *d*, *e* and *f* conformers in *trans*-2'-hydroxycyclohexyl and *trans*-2'-chlorocyclohexyl D-glucopyranosides

Compound No.	*d*	*e*	*f*
13	0.30	0.60	0.10
21	0.30	0.60	0.10
14	0.60	0.30	0.10
22	0.70	0.20	0.10
17	0.85	0.05	0.10
25	0.85	0.05	0.10
20	0.45	0.45	0.10
28	0.45	0.45	0.10

parameter for the chloro derivatives. The O/O and Cl/O parameters have been previously assigned values of ±55°. The d, e and f conformer populations for the 2'-hydroxy and 2'-chlorocyclohexyl glucosides are summarized in Table 23.

As is expected on the basis of the observed molecular rotations, the populations for conformers d, e and f are similar to those observed for the *trans*-2'-methylcyclohexyl D-glucopyranosides. The notable exception occurs in compound 14, where a difference in molecular rotation from that observed for compounds 6 and 22 was noted. The calculations show for compound 14 an increase in the population of conformer e when compared with this population in compounds 6 and 22. This can possibly be explained by the tendency to form a weak intramolecular hydrogen bond between the hydroxy substituent at C-2' and the ring oxygen atom. This would only be possible in conformer e. Similar hydrogen bonds involving the pyranoid oxygen atom have been observed in the solid state for β-D-cellobiose (19) and methyl β-D-cellobioside (71). This type of hydrogen bonding is also postulated to exist in solution between contiguous cellobiose residues in cellulose (20). However, the increase in the population of conformer e is not that substantial and, in water, the tendency to form this intramolecular hydrogen bond must be considered to be small.

As was the case with the methylcyclohexyl D-glucopyranosides, changes in the carbon-13 chemical shifts at C-1 and C-1' are evidenced for the hydroxycyclohexyl and chlorocyclohexyl D-glucopyranosides. These chemical shift changes are of the same magnitude and direction as those observed for the methylcyclohexyl derivatives. Changes in carbon-13 shifts similar to those observed for the methylcyclohexyl D-glucosides also occur at the C-6' methylene carbon atoms. The chemical shifts occurring at C-6' in the chlorocyclohexyl D-glucopyranosides may be calculated using the chemical shift values for the various methylene positions in conformers d, e and f, which were previously outlined. Since there is little difference between the observed C-6' chemical shifts for the chlorocyclohexyl and methylcyclohexyl D-glucopyranosides and their rotamer populations are similar, the calculated values for the shift at C-6' would show good agreement with the chemical shift values observed. The C-6' resonances in the hydroxycyclohexyl D-glucopyranosides are shielded slightly from those observed in their corresponding methyl- and chloro-substituted derivatives and their calculation by the method previously outlined would give poorer results.

It thus seems that the relative populations found in conformers d, e and f for all the mono-substituted cyclohexyl D-glucopyranosides are controlled simply by steric interactions involving the substituent at C-2'. A more polar substituent appears to have little effect on the conformations about the glucosidic bond system, except for compound 14, where a small shift in the conformational equilibrium between the d and e conformers was noted.

E. Conformational properties of (2'R)-*trans*-(6'S)-*trans*-Dimethylcyclohexyl D-glucopyranosides.

It has been shown that the orientation of the aglycon about the glucopyranoside linkage is dependent mainly on the steric interactions associated with an equatorial substituent vicinal to the aglyconic carbon atom. The dimethylcyclohexyl derivatives are important in understanding the conformational properties about the glucosidic bond system because these derivatives possess the configurational relationships of both the (1'R)- and (1'S)-*trans*-2'-methylcyclohexyl D-glucopyranosides. Before a consideration of the conformational equilibria involving the dimethyl derivatives, it is of interest to compare the carbon-13 spectra of the glucosidic moiety of these compounds with that of simple methyl D-glucopyranosides. The assigned chemical shifts occurring at C-2 to C-6 in (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl α- and β-glucopyranosides (32 and 30) (cf. Table 13) show little deviation from those observed for methyl α- and β-D-glucopyranosides (89).

The fact that no significant changes are observed at C-2, C-5 and C-6 in the dimethyl derivatives would necessarily rule out any of the three staggered d, e or f conformers that would direct the equatorial methyl substituent towards the hydroxy substituent at C-2 or the hydrogen and hydroxymethyl function at C-5.

The molecular rotation of (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl β-D-glucopyranoside (30), -52.3°, is remarkably similar to that observed for methyl β-D-glucopyranoside. In compound 30, the sum of the rotatory contributions from the C/O parameters will necessarily be zero, as the methyl substituent at C-6' forms a dextrarotatory screw pattern with the aglyconic oxygen atom while the methyl substituent at C-2' forms a levorotatory screw pattern with the aglyconic oxygen atom. Therefore, in order to explain the similar molecular rotation to methyl β-D-glucopyranoside by methods previously discussed, the sum of the C_o/C parameters in compound 30 must also tend to approach zero as in conformer f, or else the populations found in conformers d or e must be the same.

The conformational equilibria involving the d, e and f conformers for compound 30 are shown in Fig. 19. As shown in this figure, conformer e is unfavoured due to the steric interactions involving the methyl substituent at C-2' and the glucopyranose ring. This was shown to be

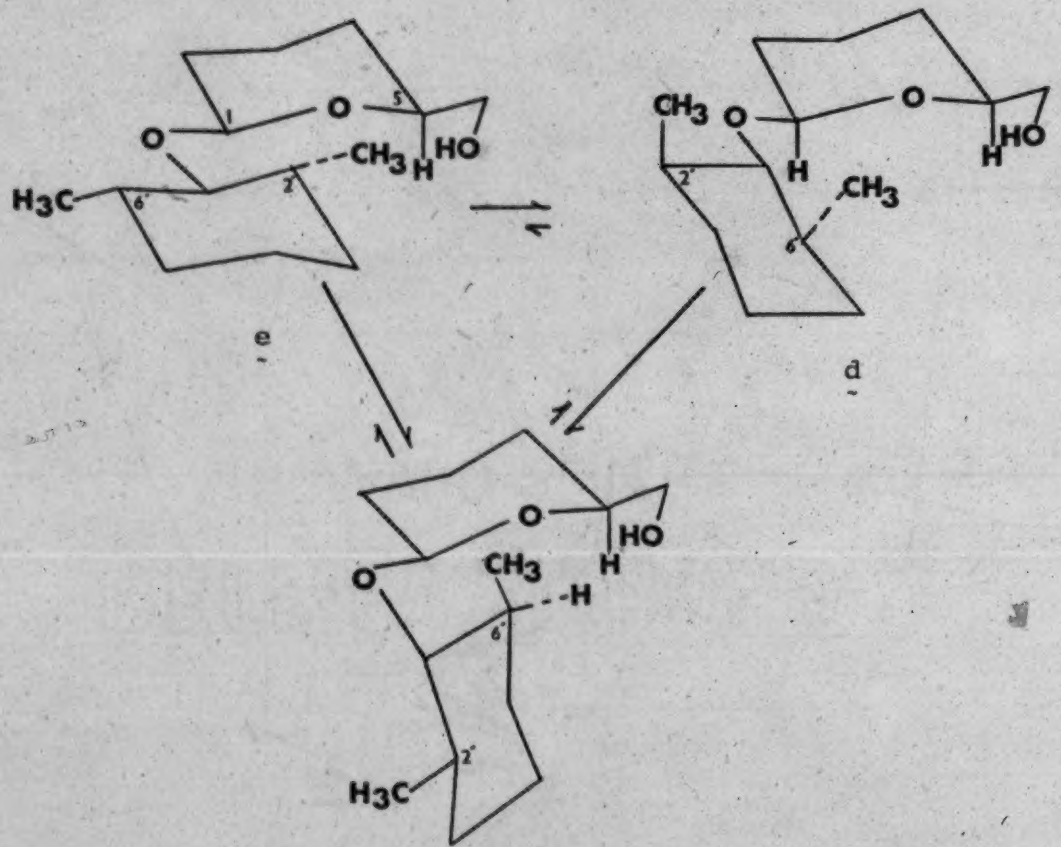

e
d
f
CH3
HO
H
H3C
O
1
5
2'
6'

Fig. 19: Conformational equilibria for (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl β-D-glucopyranoside (30).

true in the calculation of rotamer populations for compound 6. The methyl group at C-6' in conformer d is directed under the pyranose ring and severe interactions exist between the axial hydrogens at C-1 and C-5. This conformer must therefore be relatively unstable. This was evidenced in the conformational equilibrium between the d and e conformers in compound 5. In conformer f, no severe steric interactions exist between the equatorial methyl substituents and the glucopyranose ring, but some steric interaction is noted between the axial hydrogen at C-6', the ring oxygen atom and the hydroxymethyl function. However, conformer f must be predicted to exist almost exclusively in solution for (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl β-D-glucopyranoside (30) in order to explain the observed molecular rotation for this compound. Thus with di-equatorial substitution on the carbon atoms vicinal to the aglyconic carbon atom, it is apparent that the controlling preference for the orientation of the cyclohexyl aglycon about the glucosidic linkage is found in the tendency to minimize the steric interactions involving the methyl substituents. With these interactions definitely minimized in conformer f, the molecule seems content to suffer the *syn*-diaxial-like non-bonded interactions between C-2'//H-1 and C-6'//O-5 and the steric interactions involving the axial hydrogen at C-6'.

The C-1 chemical shift for compound 30 was found to be 102.7 ppm (cf. Table 13), which is not far removed from that observed for (1'S)-*trans*-2'-methylcyclohexyl β-D-glucopyranoside (5) (cf. Table 10). In both these compounds, the value of the C-1 chemical shift is deshielded relative to those observed for compounds 2 and 6, which were shown to exist largely in the d conformers.

Similar support can be derived from the calculation of the chemical shifts occurring at the C-2' and C-6' methylene positions in compound 30 which are shown below.

C-2' Methylene carbon

C//H in f (30 ppm)

$$\delta_{calc} = 1.0\ (30)$$
$$= 30\ \text{ppm}$$

$$\delta_{obs} - \alpha\text{-shift} = 37.9 - (5.6 \pm 0.4) = 32.3 \pm 0.4$$

C-6' Methylene carbon

C//O in f (35 ppm)

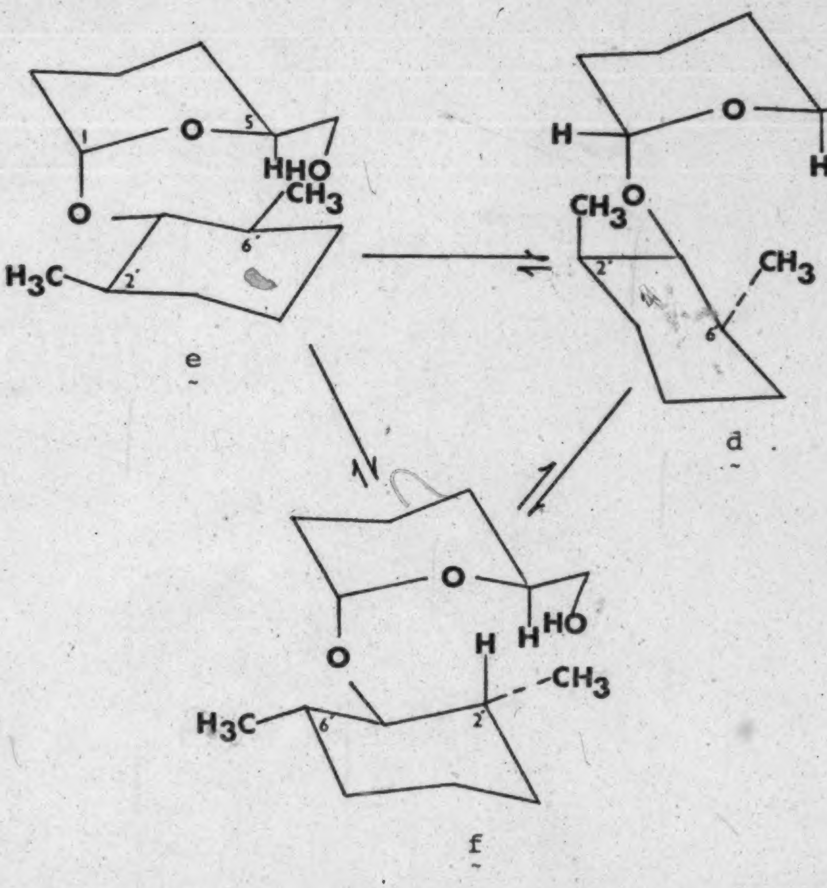
$$\delta_{calc}\quad 1.0\ (35)$$
$$= 35\ \text{ppm}$$

$$\delta_{obs} - \alpha\text{-shift} = 39.9 - (5.6 \pm 0.4) = 34.3 \pm 0.4$$

The calculated values of the chemical shifts for the C-2' and C-6' methylene carbons show reasonable agreement with that observed by taking into account the α-shift effect associated with the equatorial methyl substituent on C-2' and C-6'. This evidence from ^{13}C-n.m.r. studies, therefore, supports the trend in conformational equilibria discussed for the dimethylcyclohexyl β-D-glucopyranoside (30).

The observed molecular rotation of (2'R)-*trans*-(6'S)-trans-dimethylcyclohexyl α-D-glucopyranoside (32), 347.3°, is remarkably similar to that observed for cyclohexyl α-D-glucopyranoside (4). The conformational equilibria involving the d, e and f conformers for compound 32 are presented in Fig. 20. The calculated rotamer populations for cyclohexyl α-D-glucopyranoside (4) were as follows: 0.60d, 0.30e and 0.10 f. However, applying these rotamer populations to the conformational equilibria shown in Fig. 20 to explain the observed molecular rotation for compound 32 poses a few problems.

The large molecular rotation observed for (1'S)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (9) was explained by postulating that the severe steric interactions between the methyl substituent, the ring oxygen atom and the hydroxymethyl function made the existence of conformer e in solution negligible. The methyl group at C-6' in conformer e for compound 32 is similarly orientated and thus to assume that this conformer existed to the extent of 30% in solution is contrary to the results obtained for



1
O
5
HHO
CH3
O
6'
H3C
2'
e
H
O
H
HO
CH3
O
2'
CH3
6'
d
O
H
HO
H
O
CH3
H3C
6'
2'
f

Fig. 20: Conformational equilibria for (2'R)-*trans*-(6'S)-*trans*-dimethylcyclohexyl α-D-glucopyranoside (32)

compound 9. A consideration of the effects of substitution in conformer d reveals that the methyl group at C-2' interacts strongly with the anomeric hydrogen. A situation similar to this occurs in conformer d for (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (12), where the population of this rotamer was calculated to be 45%. Therefore, to assume that the population of conformer d is more than 45% (as is observed for cyclohexyl α-D-glucopyranoside (4)) would tend to negate the treatment of optical rotation data discussed previously for the mono-substituted cyclohexyl D-glucopyranosides. Similar to the e and d conformers, conformer f is not without interactions involving the methyl substituent. In this conformer, the equatorial methyl substituent at C-2' is directed toward the axial hydrogen and hydroxymethyl function at C-5. To summarize, the severest interaction involving methyl substituents occurs in conformer e. The probable equilibrium which, therefore, must be considered is that involving conformers d and f.

In order to explain the observed molecular rotation for compound 32 by methods previously described, the populations of conformers d and f are calculated to be, respectively, 30% and 70%. If this is indeed the case for compound 32 (the f conformer was shown to exist almost exclusively in solution for the dimethylcyclohexyl β-D-glucopyranoside (30)), then the steric interactions in conformer d must outweigh those found in conformer f.

Possible support for these calculated rotamer populations can be derived from carbon-13 chemical shift studies for compound 32. As observed in Table 13, the C-1 chemical shift was assigned at 99.1 ppm. This is similar to the 100.6 ppm chemical shift assigned to C-1 in (1'R)-*trans*-2'-methylcyclohexyl α-D-glucopyranoside (12), where the population of conformer d in solution was calculated to be 45%. The fact that the C-1 chemical shift found for compound 32 is deshielded from the values observed for compounds 4 and 9 (populations for the d conformers are, respectively, 60% and 75%) would suggest that, indeed, the relative population for conformer d must be low and nearer to that calculated for compound 12. A calculation of the chemical shifts, for the C-2' and C-6' methylene carbons is given below for compound 32.

C-2' Methylene carbon

C//H in d (30 ppm)

C//O in f (35 ppm)

$$\delta_{calc} = 0.30\ (30) + 0.70\ (35) = 33.5 \text{ ppm.}$$

$$\delta_{obs} = \alpha\text{-shift} = 39.7 - (5.6 \pm 0.4) = 34.1 \pm 0.4.$$

C-6' Methylene carbon

C//e in d (33 ppm)

C//H in f (30 ppm)

$$\delta_{calc} = 0.30\ (33) + 0.7\ (30) = 30.9$$

$$\delta_{obs} - \alpha\text{-shift} = 37.7 - (5.6 \pm 0.4) = 32.1 \pm 0.4).$$

This agreement between the observed and calculated methylene carbon chemical shifts tends to support the treatment of the possible conformational equilibria for the dimethylcyclohexyl α-D-glucopyranoside 32.

F. Optical rotation studies of cyclohexyl 6-deoxy- and *trans*-2'-methylcyclohexyl 6-deoxy-D-glucopyranosides.

These 6-deoxy derivatives were synthesized primarily to determine the contribution to molecular rotation from the *exo*-cyclic hydroxymethyl function at C-5 and assess possible effects that methyl substitution on the aglycon would have on this molecular property. A comparison between the observed molecular rotations of compounds 2, 4, 5, 6, 9 and 12 and their 6-deoxy derivatives is presented in Table 24.

In all cases reported, the hydroxymethyl grouping contributes ~ +33° to the observed molecular rotation

TABLE 24

A comparison of the observed molecular rotations for cyclohexyl and *trans*-2'-methylcyclohexyl D-glucopyranosides and their 6-deoxy derivatives

Compound	Substituent at C-5	$[M]_D^{\circ}$	$\Delta[M]_D^{\circ *}$
2	CH_2OH	-104.7°	+32.0
37	CH_3	-136.7	
5	CH_2OH	+ 28.2	+32.6
44	CH_3	- 4.4	
6	CH_2OH	-199.5	+33.2
51	CH_3	-232.7	
4	CH_2OH	+349.4	+33.2
39	CH_3	+316.2	
9	CH_2OH	+476.4	+33.2
46	CH_3	+443.1	
12	CH_2OH	+260.3	+32.5
53	CH_3	+227.8	

---

* $\Delta [M]_D^{\circ} = [M]_D^{CH_2OH} - [M]_D^{CH_3}$

of the D-glucopyranosides shown. Similar contributions to rotation are observed for the *exo*-cyclic C-5 substituent in α- and β-D-glucopyranose and their methyl D-glucopyranosides (65).

It is thus apparent that substitution on the carbon atoms vicinal to the aglyconic carbon have no effect on the orientation of the hydroxymethyl function. This supports the previous treatment of conformational equilibria for the staggered d, e and f conformers for the monosubstituted cyclohexyl D-glucopyranosides where it was shown that any conformer which directed the equatorial substituent towards the hydroxymethyl function was disfavoured.

IV CONCLUSIONS

This project has used primarily optical activity, at the D-line of sodium, to study the effects of equatorial substituents, vicinal to the aglyconic carbon, on the conformational preferences for the orientation of the cyclohexyl aglycon about the glucosidic bond system in solution. It was found that the observed molecular roations for the model compounds could be analyzed in terms of the three staggered orientations for the 6-membered aglycon using the simple empirical rules for the calculation of molecular rotation developed by Lemieux and Martin (65).

The use of carbon-13 natural abundance c.m.r. as a means of detecting conformational changes about the glycosidic bond system in solution and in the determination of rotomer populations about the aglyconic bond was demonstrated.

It was shown that substituents vicinal to the aglyconic carbon atom have a profound effect on the orientation of the 6-membered aglycon in solution. The cyclohexyl aglycon was seen to rotate about the aglyconic bond (C-1' to O-1' bond) in the direction away from large steric interactions involving these substituents. Changing the nature of the substituent in the 2' position of the aglycon from methyl, to chloro, to hydroxyl had little effect on this rotational tendency.

A small change in the conformer populations of (1'R)-

trans-2'-hydroxycyclohexyl β-D-glucopyranoside (6) was noted and was analyzed in terms of the possible formation of a weak intramolecular hydrogen bond between 0-5 and 0-2' in solution. However, since the observed change in rotamer populations was relatively small compared with that observed for derivatives with a methyl or chloro substituent in the same position, it is concluded that this type of hydrogen bond formation is negligible in polar solvents such as water.

From optical rotation studies on *trans*-2'-methylcyclohexyl 6-deoxy-D-glucopyronosides, it is concluded that the orientation of the *exo*-cyclic C-5 hydroxymethyl function is little affected by the complexity of the aglycon.

This systematic study of the conformations about the glucosidic linkage in solutions has, therefore, provided experimental evidence in support of earlier observations by Rees (3) pertaining to polysaccharide conformational analysis by the method of computer model-building.

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